

=> fil reg;d l17 ide can tot  
FILE 'REGISTRY' ENTERED AT 15:14:04 ON 05 SEP 2004  
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STRUCTURE FILE UPDATES: 3 SEP 2004 HIGHEST RN 739335-06-9  
DICTIONARY FILE UPDATES: 3 SEP 2004 HIGHEST RN 739335-06-9

TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

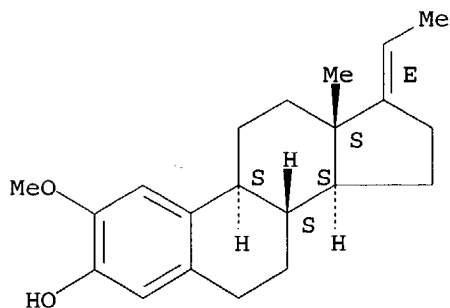
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Experimental and calculated property data are now available. For more  
information enter HELP PROP at an arrow prompt in the file or refer  
to the file summary sheet on the web at:  
<http://www.cas.org/ONLINE/DBSS/registryss.html>

L17 ANSWER 1 OF 6 REGISTRY, COPYRIGHT 2004 ACS on STN  
RN 594873-87-7 REGISTRY  
CN 19-Norpregna-1,3,5(10),17(20)-tetraen-3-ol, 2-methoxy-, (17E)-  
(9CI) (CA INDEX NAME)  
FS STEREOSEARCH  
MF C21 H28 O2  
SR CA  
LC STN Files: CA, CAPLUS  
DT.CA CAplus document type: Patent  
RL.P Roles from patents: PREP (Preparation)

Absolute stereochemistry.  
Double bond geometry as shown.



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

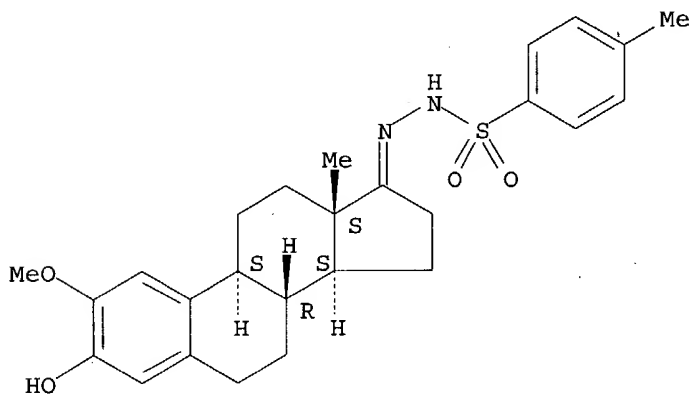
1 REFERENCES IN FILE CA (1907 TO DATE)  
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 139:224972

L17 ANSWER 2 OF 6 REGISTRY, COPYRIGHT 2004 ACS on STN  
RN 438044-29-2 REGISTRY

CN Benzenesulfonic acid, 4-methyl-, (3-hydroxy-2-methoxyestra-1,3,5(10)-trien-17-ylidene)hydrazide (9CI) (CA INDEX NAME)  
FS STEREOSEARCH  
MF C26 H32 N2 O4 S  
SR CA  
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL  
DT.CA Caplus document type: Patent  
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

Absolute stereochemistry.  
Double bond geometry unknown.



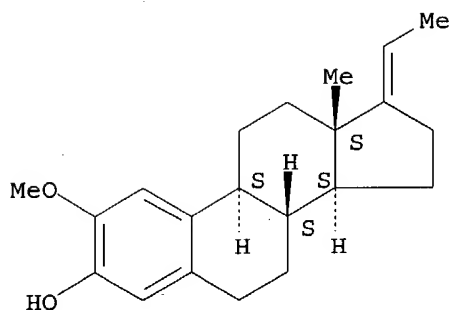
\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

1 REFERENCES IN FILE CA (1907 TO DATE)  
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 137:47357

L17 ANSWER 3 OF 6 REGISTRY COPYRIGHT 2004 ACS on STN  
RN 431901-75-6 REGISTRY  
CN 19-Norpregna-1,3,5(10),17(20)-tetraen-3-ol, 2-methoxy- (9CI)  
(CA INDEX NAME)  
FS STEREOSEARCH  
MF C21 H28 O2  
SR CA  
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL  
DT.CA Caplus document type: Patent  
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

Absolute stereochemistry.  
Double bond geometry unknown.



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

2 REFERENCES IN FILE CA (1907 TO DATE)  
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 137:47357

REFERENCE 2: 137:6309

L17 ANSWER 4 OF 6 REGISTRY COPYRIGHT 2004 ACS on STN

RN 431901-73-4 REGISTRY

CN Estradiol-1,3,5(10)-trien-3-ol, 2-methoxy-17-methylene- (9CI) (CA INDEX NAME)

FS STEREOSEARCH

MF C20 H26 O2

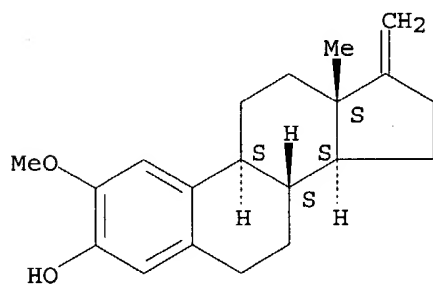
SR CA

LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

DT.CA Caplus document type: Patent

RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

Absolute stereochemistry.



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

3 REFERENCES IN FILE CA (1907 TO DATE)  
3 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:73598

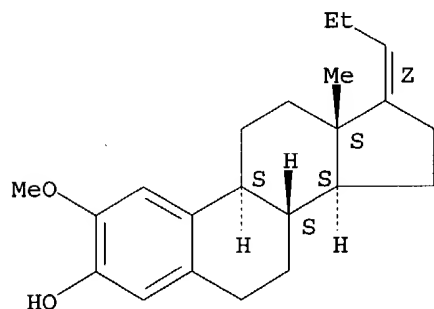
REFERENCE 2: 137:47357

REFERENCE 3: 137:6309

L17 ANSWER 5 OF 6 REGISTRY COPYRIGHT 2004 ACS on STN

RN 431901-72-3 REGISTRY  
CN **Estra-1,3,5(10)-trien-3-ol, 2-methoxy-17-propylidene-, (17Z)-**  
(9CI) (CA INDEX NAME)  
FS STEREOSEARCH  
MF C22 H30 O2  
SR CA  
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL  
DT.CA Caplus document type: Patent  
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); RACT  
(Reactant or reagent); USES (Uses)

Absolute stereochemistry.  
Double bond geometry as shown.



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

3 REFERENCES IN FILE CA (1907 TO DATE)  
3 REFERENCES IN FILE CAPLUS (1907 TO DATE)

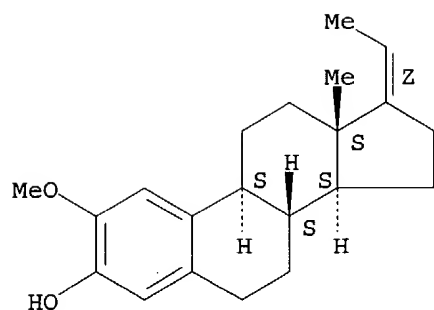
REFERENCE 1: 139:224972

REFERENCE 2: 137:47357

REFERENCE 3: 137:6309

L17 ANSWER 6 OF 6 REGISTRY COPYRIGHT 2004 ACS on STN  
RN 229486-17-3 REGISTRY  
CN **19-Norpregna-1,3,5(10),17(20)-tetraen-3-ol, 2-methoxy-, (17Z)-**  
(9CI) (CA INDEX NAME)  
FS STEREOSEARCH  
MF C21 H28 O2  
SR CA  
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL  
DT.CA Caplus document type: Patent  
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); RACT  
(Reactant or reagent)

Absolute stereochemistry.  
Double bond geometry as shown.



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

5 REFERENCES IN FILE CA (1907 TO DATE)  
5 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:73598  
REFERENCE 2: 137:370278  
REFERENCE 3: 135:358085  
REFERENCE 4: 133:350395  
REFERENCE 5: 131:88083

=> d his

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L1 1 S US20020082433/PN  
SEL RN

FILE 'REGISTRY' ENTERED AT 15:06:26 ON 05 SEP 2004  
L2 68 S E1-E68  
L3 63 S L2 AND C5-C6-C6-C6/ES  
L4 20 S L3 AND N/ELS  
L5 1 S L4 AND S/ELS  
E C26H32N2O4S/MF  
L6 2 S E3 AND C5-C6-C6-C6/ES  
L7 43 S L3 NOT L4  
L8 13 S L7 AND 2/O  
L9 3 S L8 AND (C20H26O2 OR C22H30O2 OR C21H28O2)  
E C20H26O2/MF  
L10 432 S E3 AND C5-C6-C6-C6/ES AND 4/NR  
L11 146 S L10 AND 4432.3.65/RID  
L12 1 S L11 AND 2 METHOXY AND 17 METHYLENE  
E C21H28O2/MF  
L13 152 S E3 AND 4432.3.65/RID  
L14 3 S L13 AND 2 METHOXY  
E C22H30O2/MF  
L15 110 S E3 AND 4432.3.65/RID  
L16 1 S L15 AND 2 METHOXY  
L17 6 S L5,L9,L12,L14,L16  
SEL RN  
L18 0 S E1-E6/CRN

L19 FILE 'HCAOLD' ENTERED AT 15:13:27 ON 05 SEP 2004  
0 S L17

L20 FILE 'HCAPLUS' ENTERED AT 15:13:38 ON 05 SEP 2004  
8 S L17

L21 FILE 'USPATFULL, USPAT2' ENTERED AT 15:13:42 ON 05 SEP 2004  
4 S L17

FILE 'REGISTRY' ENTERED AT 15:14:04 ON 05 SEP 2004

=> fil hcaplus

FILE 'HCAPLUS' ENTERED AT 15:14:11 ON 05 SEP 2004

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FILE COVERS 1907 - 5 Sep 2004 VOL 141 ISS 11

FILE LAST UPDATED: 3 Sep 2004 (20040903/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d l20 all hitstr tot

L20 ANSWER 1 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2004:3558 HCAPLUS

DN 140:73598

ED Entered STN: 04 Jan 2004

TI Systems and methods for rapid evaluation and design of molecules for predicted biological activity

IN Hendry, Lawrence B.

PA USA

SO U.S. Pat. Appl. Publ., 44 pp.

CODEN: USXXCO

DT Patent

LA English

IC ICM A01N001-00

NCL 435001100

CC 9-16 (Biochemical Methods)

Section cross-reference(s): 1, 3

FAN.CNT 1

|      | PATENT NO.      | KIND | DATE     | APPLICATION NO. | DATE     |
|------|-----------------|------|----------|-----------------|----------|
| PI   | US 2004002052   | A1   | 20040101 | US 2002-279546  | 20021023 |
| PRAI | US 2001-344560P | P    | 20011023 |                 |          |
|      | US 2001-339954P | P    | 20011210 |                 |          |

CLASS

PATENT NO. CLASS PATENT FAMILY CLASSIFICATION CODES

US 2004002052 ICM A01N001-00  
NCL 435001100

AB The computer-based systems and methods are for rapidly evaluating mols. for suspected biol. activity and relative potency, and for designing mols. for desired biol. activity. The systems and methods enable rapid screening of large mol. databases using one or more search engines designed to identify mols. predicted to possess specific biol. activities. Estradiol, 8 other estrogens and the conformation of the DNA site into which they fit were used to construct a search engine which was used to search databases containing a variety of compound structures.

ST system rapid evaluation design mol predicted biol activity; computer system design evaluation biol activity; large mol database search engine biol activity; estrogen search engine screening

IT Named reagents and solutions  
RL: BSU (Biological study, unclassified); BIOL (Biological study) (Horeau's acid, identified by estrogenic search engine; systems and methods for rapid evaluation and design of mols. for predicted biol. activity)

IT Antibiotics  
(against anthrax, evaluation of substances for predicted activity of; systems and methods for rapid evaluation and design of mols. for predicted biol. activity)

IT Bacillus anthracis  
(anthrax from, antibiotics against, evaluation of substances for predicted activity of; systems and methods for rapid evaluation and design of mols. for predicted biol. activity)

IT Electrostatic potential  
(between mol. and binding site, in creating search engine; systems and methods for rapid evaluation and design of mols. for predicted biol. activity)

IT Nucleic acids  
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)  
(creating search engines for mols. binding specified sites in; systems and methods for rapid evaluation and design of mols. for predicted biol. activity)

IT Penis  
(erectile activity, evaluation of substances for; systems and methods for rapid evaluation and design of mols. for predicted biol. activity)

IT Angiogenesis inhibitors  
Antidepressants  
Antidiabetic agents  
Carcinogens  
Hypnotics and Sedatives  
Selective estrogen receptor modulators  
(evaluation of substances for predicted activity of; systems and methods for rapid evaluation and design of mols. for predicted biol. activity)

IT Androgens  
Estrogens  
Glucocorticoids  
Progestogens  
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)  
(evaluation of substances for predicted activity of; systems and methods for rapid evaluation and design of mols. for predicted biol. activity)

IT Bone  
Thyroid gland  
(evaluation of substances for predicted activity on; systems and methods for rapid evaluation and design of mols. for predicted biol. activity)

IT Sexual behavior

- (impotence, evaluation of substances for predicted erectile activity, and treatment of; systems and methods for rapid evaluation and design of mols. for predicted biol. activity)
- IT Databases  
(large mol., systems and methods and search engines for rapid screening of; systems and methods for rapid evaluation and design of mols. for predicted biol. activity)
- IT Information systems  
(network; systems and methods for rapid evaluation and design of mols. for predicted biol. activity)
- IT Information systems  
(searching; systems and methods for rapid evaluation and design of mols. for predicted biol. activity)
- IT Apparatus  
Bioinformatics  
Computer program  
Computers  
Conformation  
Data processing  
Design  
Drug design  
Excluded volume  
Functional groups  
Hydrogen bond  
Molecular shape  
Molecular surface  
Molecules  
Simulation and Modeling, biological  
Simulation and Modeling, physicochemical  
Structure-activity relationship  
Volume  
(systems and methods for rapid evaluation and design of mols. for predicted biol. activity)
- IT DNA  
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)  
(systems and methods for rapid evaluation and design of mols. for predicted biol. activity)
- IT 388075-75-0, PDC 7  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(PDC 7, identified by estrogenic search engine; systems and methods for rapid evaluation and design of mols. for predicted biol. activity)
- IT 58-22-0, Testosterone 434-22-0, 19-Nortestosterone 521-11-9, 17 $\alpha$ -Methyl-5 $\alpha$ -dihydrotestosterone 521-18-6, 5 $\alpha$ -Dihydrotestosterone 1434-85-1, 5 $\alpha$ -Dihydro-19-nortestosterone 3704-07-2, 7 $\alpha$ -Methyl-5 $\alpha$ -dihydrotestosterone 3704-08-3, 3764-87-2, 7 $\alpha$ -Methyl-19-nortestosterone 6424-04-0 7642-58-2, 7 $\alpha$ -Methyltestosterone 31025-34-0  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(as standard in construction of search engine for evaluation of substances for predicted androgenic activity; systems and methods for rapid evaluation and design of mols. for predicted biol. activity)
- IT 389-08-2, Nalidixic acid 70458-92-3, Pefloxacin 70458-96-7, Norfloxacin 79660-72-3, Fleroxacin 85721-33-1, Ciprofloxacin 98079-51-7, Lomefloxacin 100986-85-4, Levofloxacin 110871-86-8, Sparfloxacin 112811-59-3, Gatifloxacin 147059-72-1, Trovafloxacin 151096-09-2, Moxifloxacin  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(as standard in construction of search engine for evaluation of substances for predicted anthrax antibiotic activity; systems and methods for rapid evaluation and design of mols. for predicted biol. activity)
- IT 362-07-2, 2-Methoxyestradiol 165619-07-8, 2-Ethoxyestradiol 192062-02-5 229486-17-3 431901-73-4 431901-98-3



431902-09-9

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(as standard in construction of search engine for evaluation of substances  
for predicted antiangiogenic activity; systems and methods for rapid  
evaluation and design of mols. for predicted biol. activity)

IT 50-48-6, Amitriptyline 50-49-7, Imipramine 303-49-1 5560-72-5,  
Iprindole 10262-69-8, Maprotiline 24526-64-5, Nomifensin 54910-89-3,  
Fluoxetine 79617-96-2, Sertraline

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(as standard in construction of search engine for evaluation of substances  
for predicted antidepressant activity; systems and methods for rapid  
evaluation and design of mols. for predicted biol. activity)

IT 50-28-2, Estradiol, biological studies 57-63-6, 17 $\alpha$ -  
Ethinylestradiol 4567-67-3, 17 $\alpha$ -Chloroethinylestradiol  
21507-14-2, 11 $\beta$ -Methoxyestradiol 34816-55-2, Moxestrol 95258-49-4  
95258-51-8 108887-25-8 130929-98-5 164580-56-7

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(as standard in construction of search engine for evaluation of substances  
for predicted estrogenic activity; systems and methods for rapid  
evaluation and design of mols. for predicted biol. activity)

IT 50-23-7, Cortisol

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(as standard in construction of search engine for evaluation of substances  
for predicted glucocorticoid activity; systems and methods for rapid  
evaluation and design of mols. for predicted biol. activity)

IT 53-43-0, Dehydroepiandrosterone

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(as standard in construction of search engine for evaluation of substances  
for predicted penile erectile and anti-impotence activity; systems and  
methods for rapid evaluation and design of mols. for predicted biol.  
activity)

IT 516-54-1, 3 $\alpha$ , 5 $\alpha$ -Tetrahydroprogesterone 516-55-2  
23930-19-0, Alphaxalone 38398-32-2, Ganaxolone

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(as standard in construction of search engine for evaluation of substances  
for predicted sedative activity; systems and methods for rapid  
evaluation and design of mols. for predicted biol. activity)

IT 15178-66-2

RL: BSU (Biological study, unclassified); PRP (Properties); BIOL  
(Biological study)  
(dbl. stranded, as DNA binding site used in evaluation of substances  
for predicted anthrax antibiotic activity; systems and methods for  
rapid evaluation and design of mols. for predicted biol. activity)

IT 4251-20-1

RL: BSU (Biological study, unclassified); PRP (Properties); BIOL  
(Biological study)  
(dbl. stranded, as DNA binding site used in evaluation of substances  
for predicted estrogenic or androgenic or other activity; systems and  
methods for rapid evaluation and design of mols. for predicted biol.  
activity)

IT 3704-09-4, Mibolerone

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(identified by androgen search engine; systems and methods for rapid  
evaluation and design of mols. for predicted biol. activity)

IT 69-53-4, Ampicillin 28657-80-9, Cinoxacin

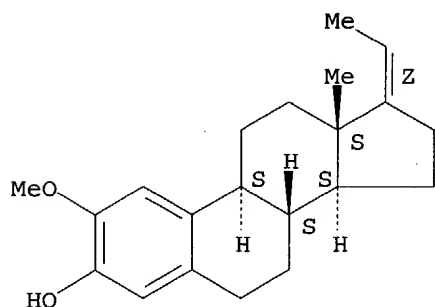
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(identified by anthrax antibiotic search engine; systems and methods  
for rapid evaluation and design of mols. for predicted biol. activity)

IT 54-32-0, Moxisylyte 56-87-1, Lysine, biological studies 74-79-3,  
Arginine, biological studies 497-76-7, Arbutin 2530-97-4, Xanthinol  
7665-99-8, Cyclic GMP

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(identified by anti-impotence search engine; systems and methods for

- rapid evaluation and design of mols. for predicted biol. activity)
- IT 117-39-5, Quercetin 501-36-0, Resveratrol 26581-81-7, EM-12  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (identified by antiangiogenic search engine; systems and methods for rapid evaluation and design of mols. for predicted biol. activity)
- IT 17692-37-4, Fantridone 34911-55-2, Bupropion 54739-18-3, Fluvoxamine 71620-89-8, Reboxetine 93413-69-5, Venlafaxine  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (identified by antidepressant search engine; systems and methods for rapid evaluation and design of mols. for predicted biol. activity)
- IT 124-87-8, Picrotoxin 5938-11-4, Callicarpone 20071-51-6, Eupatoroxin  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (identified by carcinogenic search engine; systems and methods for rapid evaluation and design of mols. for predicted biol. activity)
- IT 24643-97-8, Indenestrol  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (identified by estrogen search engine; systems and methods for rapid evaluation and design of mols. for predicted biol. activity)
- IT 56-53-1, trans-Diethylstilbestrol 446-72-0, Genistein 486-66-8, Daidzein 531-95-3, Equol 26538-44-3, Zearalanol  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (identified by estrogenic search engine; systems and methods for rapid evaluation and design of mols. for predicted biol. activity)
- IT 50-35-1, Thalidomide  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (identified by sedative and antidepressant and antiangiogenic search engines; systems and methods for rapid evaluation and design of mols. for predicted biol. activity)
- IT 21715-46-8, Etifoxine 61869-08-7, Paroxetine  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (identified by sedative and antidepressant search engines; systems and methods for rapid evaluation and design of mols. for predicted biol. activity)
- IT 57-43-2, Amobarbital 58-61-7, Adenosine, biological studies 73-31-4, Melatonin 77-26-9, Butalbital 1972-08-3, 89 Tetrahydrocannabinol 20007-85-6, Cyclophenol 57801-81-7, Brotizolam  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (identified by sedative search engine; systems and methods for rapid evaluation and design of mols. for predicted biol. activity)
- IT 229486-17-3 431901-73-4  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (as standard in construction of search engine for evaluation of substances for predicted antiangiogenic activity; systems and methods for rapid evaluation and design of mols. for predicted biol. activity)
- RN 229486-17-3 HCAPLUS
- CN 19-Norpregna-1,3,5(10),17(20)-tetraen-3-ol, 2-methoxy-, (17Z)- (9CI) (CA INDEX NAME)

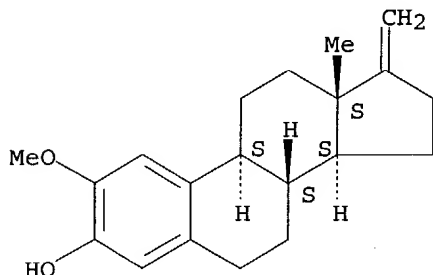
Absolute stereochemistry.  
 Double bond geometry as shown.



RN 431901-73-4 HCAPLUS

CN Estra-1,3,5(10)-trien-3-ol, 2-methoxy-17-methylene- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L20 ANSWER 2 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2003:719252 HCAPLUS

DN 139:224972

ED Entered STN: 14 Sep 2003

TI Synthesis of 2-methoxyestradiol derivatives and uses as antiangiogenic agents

IN Lavallee, Theresa M.; Pribluda, Victor S.; Simons, Jonathan; Mabjeesh, Nicola; Giannakakou, Paraskevi

PA Entremed, Inc., USA

SO PCT Int. Appl., 77 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM A61K

CC 2-4 (Mammalian Hormones)

Section cross-reference(s): 32

FAN.CNT 1

|    | PATENT NO.  | KIND | DATE     | APPLICATION NO. | DATE     |
|----|---|------|----------|-----------------|----------|
| PI | WO 2003073985   | A2   | 20030912 | WO 2003-US5898  | 20030227 |
|    | WO 2003073985   | A3   | 20031231 |                 |          |
|    | W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM |      |          |                 |          |
|    | RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG  |      |          |                 |          |

PRAI US 2002-361267P P 20020301

CLASS

PATENT NO. CLASS PATENT FAMILY CLASSIFICATION CODES

WO 2003073985 ICM A61K

AB Comps. and methods for treating mammalian disease characterized by undesirable angiogenesis and for controlling a number of angiogenesis-related events, conditions, or substances, by administering derivs. of 2-methoxyestradiol of general formula (I) wherein the variables are defined in the specification.

ST estrogen methoxyestradiol analogs angiogenesis inhibitor VEGF DR5 HIFalpha

IT Apoptosis

- (2-ME2-induced; synthesis of 2-methoxyestradiol derivs. and uses as antiangiogenic agents)
- IT Cytokine receptors  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (DR5 (death receptor 5); synthesis of 2-methoxyestradiol derivs. and uses as antiangiogenic agents)
- IT Transcription factors  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (HIF-1 $\alpha$  (hypoxia-inducible factor 1 $\alpha$ ); synthesis of 2-methoxyestradiol derivs. and uses as antiangiogenic agents)
- IT Blood vessel  
 (endothelium; synthesis of 2-methoxyestradiol derivs. and uses as antiangiogenic agents)
- IT Transcriptional regulation  
 (of HIF-1 $\alpha$ , 2-ME2-inhibited; synthesis of 2-methoxyestradiol derivs. and uses as antiangiogenic agents)
- IT Angiogenesis  
 Angiogenesis inhibitors  
 Human  
 (synthesis of 2-methoxyestradiol derivs. and uses as antiangiogenic agents)
- IT Estrogens  
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)  
 (synthesis of 2-methoxyestradiol derivs. and uses as antiangiogenic agents)
- IT 127464-60-2, Vascular Endothelial Growth Factor  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (synthesis of 2-methoxyestradiol derivs. and uses as antiangiogenic agents)
- IT 362-07-2DP, 2-Methoxyestradiol, derivs. and analogs 362-07-2P, 2-Methoxyestradiol  
 RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)  
 (synthesis of 2-methoxyestradiol derivs. and uses as antiangiogenic agents)
- IT 50-00-0, Formaldehyde, reactions 50-28-2D, Estradiol, derivs. and analogs 53-16-7, Estrone, reactions 64-18-6, Formic acid, reactions 64-19-7, Acetic acid, reactions 67-68-5, Methyl sulfoxide, reactions 68-12-2, DMF, reactions 71-36-3, 1-Butanol, reactions 75-09-2, Methylene chloride, reactions 79-37-8, Oxalyl chloride 100-39-0, Benzyl bromide 106-95-6, Allyl bromide, reactions 109-99-9, THF, reactions 111-46-6, Diethylene glycol, reactions 121-44-8, Triethylamine, reactions 141-78-6, Ethyl acetate, reactions 302-01-2, Hydrazine, reactions 362-08-3, 2-Methoxyestrone 362-08-3D, 2-Methoxyestrone, olefin analogs 584-08-7, Potassium carbonate 1157-87-5, AH3 1530-32-1, Ethyl triphenylphosphonium bromide 1779-49-3, Methyltriphenylphosphonium bromide 1779-51-7, Butyl triphenylphosphonium bromide 4111-54-0, Lithium diisopropyl amide 4784-77-4, Crotyl bromide 5815-08-7, tert-Butoxy bis(dimethylamino)methane 6228-47-3, Propyl triphenylphosphonium bromide 7447-41-8, Lithium chloride, reactions 7632-00-0, Sodium nitrite 7693-26-7, Potassium hydride 16853-85-3, Lithium aluminum hydride 17455-13-9, 18-Crown-6 17640-15-2, Methyl cyanoformate 41233-93-6, Potassium-tert-amylate 431901-79-0 431901-81-4 431901-84-7 431901-85-8 431901-89-2  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (synthesis of 2-methoxyestradiol derivs. and uses as antiangiogenic agents)
- IT 53-63-4P, Estra-1,3,5(10)-trien-3-ol  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(synthesis of 2-methoxyestradiol derivs. and uses as antiangiogenic agents)

IT 362-07-2DP, 2-Methoxyestradiol, alkyl analogs 4953-96-2P 6298-51-7P  
6301-87-7P 6599-97-9P 7291-57-8P 10332-20-4P 26356-54-7DP, alkyl  
derivs 26356-54-7DP, alkyl derivs. 26356-54-7P 26357-07-3DP,  
16 $\alpha$ -alkyl derivs. 26357-07-3P 32162-96-2P 34111-53-0P  
93949-26-9P 165619-07-8P 229486-18-4P 431901-68-7P 431901-69-8P  
431901-70-1P 431901-71-2P **431901-72-3P** 431901-77-8P  
431901-78-9P 431901-80-3DP, alkyl derivs. 431901-89-2DP, alkyl analogs  
431901-90-5P 431901-91-6P 431901-92-7P 431901-93-8P 431901-98-3P  
431901-99-4P 431902-01-1P 431902-02-2P 431902-03-3P 431902-04-4P  
431902-05-5P 431902-06-6P 431902-09-9P 438044-30-5P 464924-32-1P  
594873-85-5P 594873-86-6P **594873-87-7P**

RL: SPN (Synthetic preparation); PREP (Preparation)

(synthesis of 2-methoxyestradiol derivs. and uses as antiangiogenic agents)

IT **431901-72-3P 594873-87-7P**

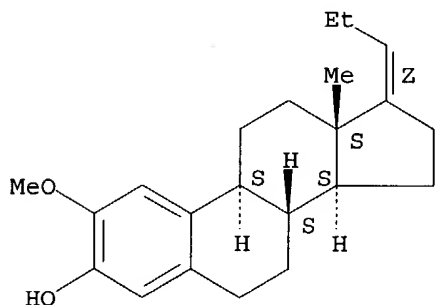
RL: SPN (Synthetic preparation); PREP (Preparation)

(synthesis of 2-methoxyestradiol derivs. and uses as antiangiogenic agents)

RN 431901-72-3 HCAPLUS

CN Estr-1,3,5(10)-trien-3-ol, 2-methoxy-17-propylidene-, (17Z)- (9CI) (CA INDEX NAME)

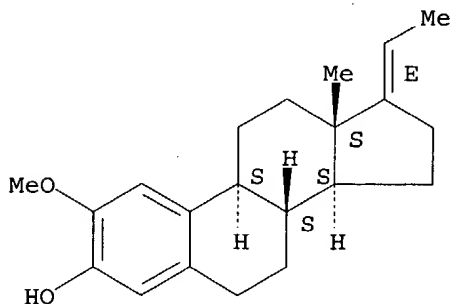
Absolute stereochemistry.  
Double bond geometry as shown.



RN 594873-87-7 HCAPLUS

CN 19-Norpregna-1,3,5(10),17(20)-tetraen-3-ol, 2-methoxy-, (17E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.  
Double bond geometry as shown.



DN 137:370278  
 ED Entered STN: 22 Nov 2002  
 TI Preparation of substituted pregna-1,3,5(10)-triene derivatives for pharmaceutical use  
 IN Hesse, Robert Henry; Setty, Sundara Katugam Srinivasasetty; Pechet, Maurice Murdoch; Gile, Michael  
 PA Marsden, John Christopher, UK; Research Institute for Medicine and Chemistry Inc.  
 SO PCT Int. Appl., 28 pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
 IC ICM A61K031-56  
 ICS A61K031-575; C07J041-00; A61P035-00  
 CC 32-5 (Steroids)  
 Section cross-reference(s): 1, 2, 63

FAN.CNT 1

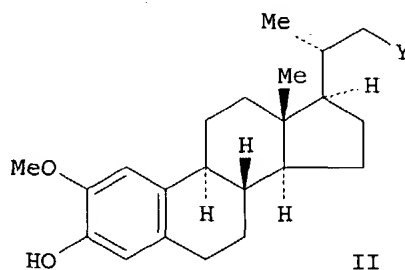
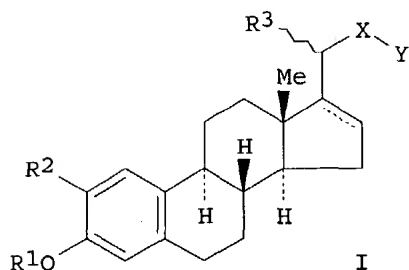
| PATENT NO.  | KIND | DATE     | APPLICATION NO. | DATE     |
|---|------|----------|-----------------|----------|
| WO 2002092100   | A1   | 20021121 | WO 2002-GB2210  | 20020513 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM<br>RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG |      |          |                 |          |
| PRAI US 2001-290013P  | P    | 20010511 |                 |          |

CLASS

| PATENT NO.    | CLASS | PATENT FAMILY CLASSIFICATION CODES  |
|---------------|-------|-------------------------------------|
| WO 2002092100 | ICM   | A61K031-56                          |
|               | ICS   | A61K031-575; C07J041-00; A61P035-00 |

OS MARPAT 137:370278

GI



AB Pregna-1,3,5(10)-triene derivs., such as I [R1 = H, hydroxy protecting group; R2 = OH, CHO, alkoxy, alkenyl, alkyl, etc.; R3 =  $\alpha$ -,  $\beta$ -Me; X = C1-3 alkylene group, bond; Y = C(R4)(R5)NR6R7; R4, R5 = H, alkyl, alkenyl and alkynyl groups, such that the total carbon content of R4 and R5 does not exceed three atoms; R6 = H, aliphatic or araliph. organic group, acyl, etc.; C16-C17 = saturated, unsatd.], were prepared for a variety of therapeutic uses, such as modulating cell activity, including

antiproliferative and antiangiogenic effects. Thus, pregna-1,3,5(10)-triene derivs. II (Y = NH<sub>2</sub>, NHCOMe) were prepared via a multistep synthetic series starting from 2-methoxy-3-[[tris(1-methylethyl)silyl]oxy]-estra-1,3,5(10)-trien-17-one and ethyltriphenylphosphonium bromide. Pharmaceutical compns. of the prepared compds. were discussed, but specific pharmaceutical activity testing data was not presented.

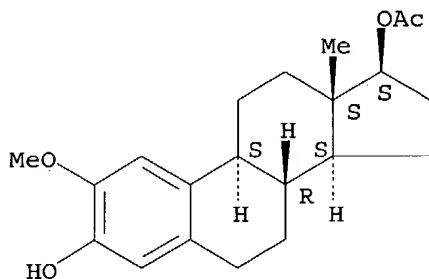
- ST norpregnatriene prepn antiproliferative antiangiogenic agent
- IT Mental disorder  
(cognitive, treatment; preparation of substituted pregna-1,3,5(10)-triene derivs. for a variety of therapeutic uses)
- IT Blood coagulation  
Cognition  
(disorder, treatment; preparation of substituted pregna-1,3,5(10)-triene derivs. for a variety of therapeutic uses)
- IT Transplant and Transplantation  
(graft-vs.-host reaction, treatment; preparation of substituted pregna-1,3,5(10)-triene derivs. for a variety of therapeutic uses)
- IT Anti-inflammatory agents  
Anticholesteremic agents  
Antitumor agents  
Cognition enhancers  
Contraceptives  
Immunomodulators  
(preparation of substituted pregna-1,3,5(10)-triene derivs. for a variety of therapeutic uses)
- IT Arthritis  
(psoriatic arthritis, treatment; preparation of substituted pregna-1,3,5(10)-triene derivs. for a variety of therapeutic uses)
- IT Mental disorder  
(senile psychosis, treatment; preparation of substituted pregna-1,3,5(10)-triene derivs. for a variety of therapeutic uses)
- IT Asthma  
Autoimmune disease  
Bone, disease  
Hypercholesterolemia  
Hyperplasia  
Hypertension  
Inflammation  
Neoplasm  
Rheumatoid arthritis  
Skin, disease  
Transplant rejection  
(treatment; preparation of substituted pregna-1,3,5(10)-triene derivs. for a variety of therapeutic uses)
- IT 4736-60-1, Ethyltriphenylphosphonium iodide 305812-67-3  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(preparation of substituted pregna-1,3,5(10)-triene derivs. for a variety of therapeutic uses)
- IT 229486-17-3P 305812-87-7P 305812-99-1P 372952-47-1P  
372952-49-3P 372952-50-6P 475486-81-8P 475486-82-9P 475486-83-0P  
475486-84-1P  
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
(preparation of substituted pregna-1,3,5(10)-triene derivs. for a variety of therapeutic uses)
- IT 475486-79-4P 475486-80-7P  
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(preparation of substituted pregna-1,3,5(10)-triene derivs. for a variety of therapeutic uses)
- RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
- RE  
(1) Christopher, M; WO 0068246 A 2000 HCAPLUS

1,3,5(10)-estratriene 3-(2-benzoyl-4-nitro)phenyl ether (VIII), m. 132-44° (MeOH),  $\lambda$  255, 287 m $\mu$ ,  $\epsilon$  16,000 and 11,000. Acetylation of VIII with Ac<sub>2</sub>O in C<sub>5</sub>H<sub>5</sub>N gave 16 $\alpha$ ,17 $\beta$ -diacetoxy-1,3,5(10)-estratriene 3-(2-benzoyl-4-nitro)phenyl ether (IX), m. 74-6° (AcOH), no OH absorption at 3600 cm.<sup>-1</sup> IX (1 g.) in 2 cc. AcOH and 2 cc. cold concentrated H<sub>2</sub>SO<sub>4</sub> left 0.5 hr. at room temperature, diluted with 15 ml. AcOH, excess 30% H<sub>2</sub>O<sub>2</sub> added, the solution left 0.5 hr. longer, poured into H<sub>2</sub>O, the solid collected, and dried gave 750 mg. 2-hydroxy-16 $\alpha$ ,17 $\beta$ -diacetoxy-1,3,5(10)-estratriene 3-(2-benzoyl-4-nitro)phenyl ether (X),  $\nu$  1655 cm.<sup>-1</sup> X (0.7 g.) in a min. amount of alc.-Et<sub>2</sub>O left 24 hrs. with excess CH<sub>2</sub>N<sub>2</sub>, and the solvents evaporated gave 2-methoxy-16 $\alpha$ ,17 $\beta$ -diacetoxy-1,3,5(10)-estratriene 3-(2-benzoyl-4-nitro)phenyl ether (XI), m. 155-8° (MeOH),  $\nu$  1672 cm.<sup>-1</sup> XI (0.6 g.) refluxed 1 hr. under N with 6% alc.-KOH, acidified, and extracted with CHCl<sub>3</sub>-Et<sub>2</sub>O followed by countercurrent distribution in a system of 50% aqueous MeOH and 1:1 cyclohexane-EtOAc gave 180 mg. I, m. 211-14° (dilute Me<sub>2</sub>CO),  $[\alpha]_{26D}$  83° (alc.),  $\lambda$  286 and 253 m $\mu$ ,  $\epsilon$  3500 and 350. IX (5 g.) cyclized and oxidized as above gave the 2-OH product, which, dissolved in alkali, left 15 min., acidified, the product reextd., the crude material taken up in alc., treated with ethereal CH<sub>2</sub>N<sub>2</sub>, and the product, m. 160-90°, reacetylated, the total material refluxed 1.5 hrs. in 60 cc. piperidine under N, the solution diluted with 250 cc. C<sub>6</sub>H<sub>6</sub>, washed, and the residue chromatographed on Al<sub>2</sub>O<sub>3</sub> gave 0.6 g. 16,17-diacetate of the 3-Me ether of II (XII), m. 178-81° (C<sub>6</sub>H<sub>6</sub>-ligroine),  $[\alpha]_{27D}$  -16.5°. Preceding chromatographic fractions were oils which on hydrolysis with 5% alc.-KOH gave 1 g. 2-methoxyestriol (XIII). XII (0.5 g.) on hydrolysis in 5% alc.-KOH gave 230 mg. III, m. 268-71° (MeOH-C<sub>6</sub>H<sub>6</sub>),  $[\alpha]_{25D}$  64°. III by methylation with CH<sub>2</sub>N<sub>2</sub> gave 3-Me ether of 2-methoxyestriol (XIV), m. 190-2° (Me<sub>2</sub>CO-ligroine),  $[\alpha]_{27D}$  69°. Similar methylation of XIII gave XIV. 2-Hydroxy-17-acetoxy-1,3,5(10)-estratriene 3-(2-benzoyl)phenyl ether (XIVa) (8 g.) in Claisen alkali left 15 min. at room temperature, the whole acidified and extracted with CHCl<sub>3</sub> gave a crude mixture, which was methylated with CH<sub>2</sub>N<sub>2</sub>, the methylated product reacetylated and then refluxed 1 hr. in 100 ml. piperidine, and chromatographed on Al<sub>2</sub>O<sub>3</sub>, to give 1 g. 2-methoxyestradiol, 17-acetate (XV). With 50% C<sub>6</sub>H<sub>6</sub>-ligroine, 3.1 g. 2-hydroxyestradiol, 3-Me ether 17-acetate (XVI), m. 210-12° (C<sub>6</sub>H<sub>6</sub>-ligroine),  $[\alpha]_{27D}$  43.0° was obtained. XVI (1 g.) hydrolyzed in the usual way with 5% alc.-KOH gave 0.85 g. IV, m. 179-81° (Me<sub>2</sub>CO),  $[\alpha]_{28D}$  74°. Methylation of XVI with Et<sub>2</sub>O-CH<sub>2</sub>N<sub>2</sub> gave 2-methoxyestradiol 3-Me ether 17-acetate (XVII), m. 179-82° (alc.),  $[\alpha]_{27D}$  53°. A similar methylation of XV gave XVII. Hydrolysis of XVII with MeOH-KOH gave 2-methoxyestradiol 3-Me ether (XVIII), m. 131-3° (MeOH-Et<sub>2</sub>O),  $[\alpha]_{27D}$  85°. Oxidation of a small amount of XVIII with CrO<sub>3</sub> in Me<sub>2</sub>CO gave VI, needles, m. 173-6°. VI was also obtained by methylation of 2-methoxyestrone (XIX). VI (1 g.) heated 15 min. at 200-20° with 2 g. freshly distilled C<sub>5</sub>H<sub>5</sub>N, diluted with H<sub>2</sub>O, and extracted with CHCl<sub>3</sub>-alc. gave 700 mg. crude IV, m. 155-8°,  $[\alpha]_{28D}$  90° (alc.),  $\lambda$  289 m $\mu$ ,  $\epsilon$  3600. IV was also obtained by an alternate route from XIVa. Piperidine cleavage of XIVa gave 17-acetate of IV, m. 182-5°,  $[\alpha]_{26D}$  59°. Acid hydrolysis of IV 17-acetate gave IV. XIX (100 mg.) heated with C<sub>5</sub>H<sub>5</sub>N.HCl as above and the mixture diluted with H<sub>2</sub>O gave 63 mg. VII, m. 194-6° (C<sub>6</sub>H<sub>6</sub>),  $[\alpha]_{27D}$  172° (alc.). VII was obtained from either I or III on heating 1 hr. at 200° with C<sub>5</sub>H<sub>5</sub>N.HCl. An alternative route led via the Schotten-Baumann benzylation of IV to give the dibenzoate which on oxidation with CrO<sub>3</sub> in AcOH gave VII 2,3-dibenzoate, m. 172-4° (alc.). Mild hydrolysis of the above under N gave VII. C<sub>5</sub>H<sub>5</sub>N.HCl-fusion of 200 mg. 3-Me ether of 4-hydroxyestrone gave 138 mg. 4-hydroxyestrone, m. 260-5° (C<sub>6</sub>H<sub>6</sub>-MeOH),  $[\alpha]_{27D}$  155° (alc.).



- IT Infrared spectra  
Ultraviolet and visible, spectra  
(of estra-1,3,5(10)-triene-2,3-diol derivs.)
- IT Estra-1,3,5(10)-trien-17 $\beta$ -ol, 2,3-dimethoxy-, compound with methanol  
Estra-1,3,5(10)-triene-16 $\alpha$ ,17 $\beta$ -diol, 3-(2-benzoyl-4-nitrophenoxy)-  
Estra-1,3,5(10)-triene-16 $\alpha$ ,17 $\beta$ -diol, 3-(2-benzoyl-4-nitrophenoxy)-, diacetate  
Estra-1,3,5(10)-triene-16 $\alpha$ ,17 $\beta$ -diol, 3-(2-benzoyl-4-nitrophenoxy)-2-methoxy-, diacetate  
Estra-1,3,5(10)-triene-2,16 $\alpha$ ,17 $\beta$ -triol, 3-(2-benzoyl-4-nitrophenoxy)-, 16,17-diacetate  
Methanol, compound with 2,3-dimethoxyestra-1,3,5(10)-trien-17 $\beta$ -ol
- IT Estra-1,3,5(10)-triene-2,3-diol  
(derivs.)
- IT 362-05-0, Estra-1,3,5(10)-triene-2,3,17 $\beta$ -triol 362-06-1,  
Estra-1,3,5(10)-trien-17-one, 2,3-dihydroxy- 1236-72-2, Estriol,  
2-methoxy- 3131-23-5, Estra-1,3,5(10)-trien-17-one, 3,4-dihydroxy-  
5976-64-7, Estra-1,3,5(10)-trien-17-one, 2,3-dimethoxy- 5976-65-8,  
Estra-1,3,5(10)-triene-2,17 $\beta$ -diol, 3-methoxy- 5976-67-0,  
Estra-1,3,5(10)-trien-17 $\beta$ -ol, 2,3-dimethoxy- 5976-70-5,  
Estra-1,3,5(10)-trien-17 $\beta$ -ol, 2,3-dimethoxy-, acetate 21696-98-0,  
Estra-1,3,5(10)-triene-16 $\alpha$ ,17 $\beta$ -diol, 2,3-dimethoxy-  
23463-05-0, Estra-1,3,5(10)-triene-2,3,17 $\beta$ -triol, 17-acetate  
28818-82-8, Estra-1,3,5(10)-triene-2,16 $\alpha$ ,17 $\beta$ -triol, 3-methoxy-  
52717-98-3, Estradiol, 2-methoxy-, 17-acetate 52717-99-4,  
Estra-1,3,5(10)-triene-2,17 $\beta$ -diol, 3-methoxy-, 17-acetate  
59495-33-9, Estra-1,3,5(10)-triene-2,16 $\alpha$ ,17 $\beta$ -triol, 3-methoxy-,  
16,17-diacetate 116282-36-1, Estra-1,3,5(10)-trien-17-one,  
2,3-dihydroxy-, dibenzoate 117921-01-4, Benzophenone,  
2-(16 $\alpha$ ,17 $\beta$ -dihydroxyestra-1,3,5(10)-trien-3-yloxy)-5-nitro-  
121212-59-7, Benzophenone, 2-(16 $\alpha$ ,17 $\beta$ -dihydroxyestra-1,3,5(10)-  
trien-3-yloxy)-5-nitro-, diacetate 122426-55-5, Benzophenone,  
2-(16 $\alpha$ ,17 $\beta$ -dihydroxy-2-methoxyestra-1,3,5(10)-trien-3-yloxy)-5-nitro-, diacetate  
(preparation of)
- IT 52717-98-3, Estradiol, 2-methoxy-, 17-acetate  
(preparation of)
- RN 52717-98-3 HCAPLUS
- CN Estra-1,3,5(10)-triene-3,17-diol, 2-methoxy-, 17-acetate, (17 $\beta$ )-  
(9CI) (CA INDEX NAME)

Absolute stereochemistry.

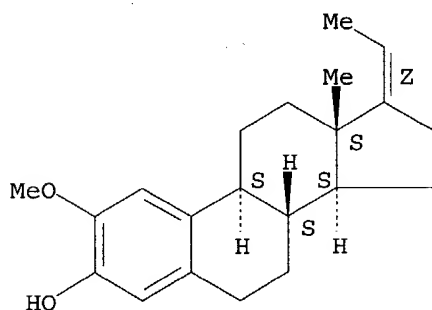


L30 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2004 ACS on STN  
AN 1958:77293 HCAPLUS  
DN 52:77293  
OREF 52:13765i,13766a-h  
ED Entered STN: 22 Apr 2001  
TI Synthesis of 2-methoxyestrogens

AU Fishman, Jack  
CS Sloan-Kettering Inst. for Cancer Research, New York, NY  
SO Journal of the American Chemical Society (1958), 80, 1213-16  
CODEN: JACSAT; ISSN: 0002-7863  
DT Journal  
LA Unavailable.  
CC 10 (Organic Chemistry)  
OS CASREACT 52:77293  
AB Estrone (I) (1.71 g.) added to 0.210 g. KOH in 50 cc. absolute EtOH, warmed, treated with 0.853 g. 2,5-Cl(O2N)C6H3Bz (II), refluxed 24 hrs., concentrated to half the original volume, cooled, poured into N NaOH, extracted with CHCl3, and the extract evaporated yielded 1.365 g. 3-(2-benzoyl-4-nitrophenyl) ether (III) of I, m. 240-3° (MeOH),  $[\alpha]_{26D}$  88°; the aqueous alkaline solution acidified gave 0.7 g. unchanged I. III (100 mg.) in 0.5 cc. cold. concentrated H2SO4 treated after 0.5 hr. with 4 cc. glacial AcOH then with 0.5 cc. 30% H2O2, allowed to stand 0.5 hr., poured into iced H2O, filtered, the solid washed with H2O, treated with excess CH2N2 in Et2O, the resulting needles, m. 144-7°, refluxed 1 hr. with piperidine, diluted with C6H6, washed with dilute H2SO4, the C6H6 layer extracted with dilute aqueous NaOH, and the aqueous extract acidified and extracted with CHCl3 gave a few crystals of the 13,17-secolactone, m. 204-7°. 17 $\beta$ -Estradiol (IV) (5 g.) and 0.586 g. KOH in 100 cc. EtOH refluxed 48 hrs. with 2.4 g. II, concentrated to half the original volume, poured into 200 cc. N NaOH, extracted with CHCl3, the extract dried, evaporated, and the residual viscous oil dissolved in 50 cc. 1:1 petr. ether-C6H6 and chromatographed on 150 g. Al2O3 gave 90 mg. II, m. 114-16°, and 4.12 g. 3,17 $\beta$ -dihydroxy-1,3,5-(10)-estratriene 3-(2-benzoyl-4-nitrophenyl) ether (V), m. 97-105°,  $[\alpha]_{26D}$  40°. V was oxidized in excellent yield to III. Further elution of the column with Et2O gave some unreacted IV. V with Ac2O and pyridine gave the acetate (VI) of V, viscous oil. VI (7.5 g.) in 4 cc. glacial AcOH treated slowly with cooling and shaking with 10 cc. cold concentrated H2SO4, kept 0.5 hr. at room temperature, diluted with 40 cc. glacial AcOH, treated dropwise with 10 cc. 1:1 AcOH-30% H2O2, kept 0.5 hr. at room temperature, poured into iced H2O, and filtered gave 4.6 g. 2-OH derivative (VII) of VI, m. 170-2° (MeOH),  $[\alpha]_{28.8D}$  21.0°; 2nd crop, 1.6 g. VII (2.2 g.) in 50 cc. EtOH kept 24 hrs. at 5° with excess CH2N2 in Et2O and evaporated gave 2 g. 2-MeO analog (VIII) of VII, m. 169-71°,  $[\alpha]_{26D}$  36°. VIII (432 mg.) refluxed 1 hr. in 20 cc. pyridine, diluted with 100 cc. C6H6, washed with dilute H2SO4 and N NaOH, evaporated, and the oily residue (446 mg.) chromatographed on 16 g. Al2O3 yielded 180 mg. 2-methoxy-3-hydroxy-17 $\beta$ -acetoxy-1,3,5(10)-estratriene (IX), plates changing to needles, m. 194-6° (C6H6-petr. ether),  $[\alpha]_{26D}$  125°. IX hydrolyzed under N with 5% alc. KOH gave 2-methoxy-17 $\beta$ -estradiol (X), m. 184-6° (C6H6). VIII (1.43 g.) in 50 cc. 6% alc. KOH refluxed 2 hrs. under N, diluted with H2O, and extracted with C6H6 gave 700 mg. X, blades, m. 188-90° (Me2CO),  $[\alpha]_{21D}$  100°; diacetate of X, needles, m. 165-6° (MeOH),  $[\alpha]_{26.5D}$  53°. X partially dissolved in N NaOH and shaken with excess BzCl gave 3-monobenzoate (XI) of X, m. 195-8° (MeOH),  $[\alpha]_{28D}$  72°. VIII (203 mg.) in 40 cc. EtOH containing 8 cc. concentrated H2SO4 refluxed 24 hrs., diluted with H2O, extracted with Et2O, and the extract worked up gave 180 mg. 2-MeO derivative (XII) of V, m. 125-6° (MeOH),  $[\alpha]_{28D}$  61°, also obtained in considerably lower yield by alkaline hydrolysis of VIII at room temperature XII (290 mg.) in 40 cc. Me2CO treated dropwise with 8N CrO3-H2SO4 until an orange-brown color persisted, kept 15 min. at room temperature, poured into H2O, and extracted with CHCl3 yielded 231 mg. 2-MeO derivative (XIII) of I, needles, m. 204-5° (MeOH),

(2) Christopher, M; WO 0185755 A 2001 HCAPLUS  
 (3) Cushman, M; JOURNAL OF MEDICINAL CHEMISTRY 1995, V38(12), P2041 HCAPLUS  
 (4) Jacques, P; US 3291690 A 1966  
 IT 229486-17-3P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
 (Reactant or reagent)  
 (preparation of substituted pregna-1,3,5(10)-triene derivs. for a variety of  
 therapeutic uses)  
 RN 229486-17-3 HCAPLUS  
 CN 19-Norpregna-1,3,5(10),17(20)-tetraen-3-ol, 2-methoxy-, (17Z)- (9CI) (CA  
 INDEX NAME)

Absolute stereochemistry.  
 Double bond geometry as shown.



L20 ANSWER 4 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN  
 AN 2002:488275 HCAPLUS  
 DN 137:47357  
 ED Entered STN: 28 Jun 2002  
 TI Preparation of 2-methoxyestradiol derivatives as antiangiogenic agents  
 IN Agoston, Gregory E.; Shah, Jamshed H.; Hunsucker, Kimberly A.; Pribluda,  
 Victor S.; Lavalley, Theresa M.; Green, Shawn J.; Herbstritt, Christopher  
 J.; Zhan, Xiaoguo H.; Treston, Anthony M.  
 PA USA  
 SO U.S. Pat. Appl. Publ., 37 pp., Cont.-in-part of U. S. Ser. No. 933,894.  
 CODEN: USXXCO  
 DT Patent  
 LA English  
 IC ICM C07J041-00  
 ICS C07J043-00; C07J001-00; A61K031-704; A61K031-58; A61K031-56;  
 C07C247-00; A61K031-655; C07J009-00  
 NCL 552544000  
 CC 32-3 (Steroids)  
 Section cross-reference(s): 1

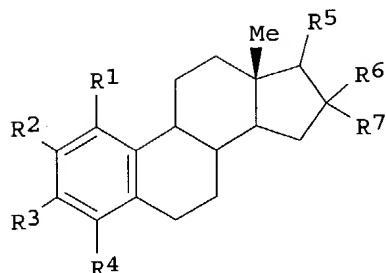
FAN.CNT 2

|      | PATENT NO.      | KIND | DATE     | APPLICATION NO. | DATE     |
|------|-----------------|------|----------|-----------------|----------|
| PI   | US 2002082433   | A1   | 20020627 | US 2001-939208  | 20010824 |
| PRAI | US 2000-641327  | A2   | 20000818 |                 |          |
|      | US 2000-253385P | P    | 20001127 |                 |          |
|      | US 2000-255302P | P    | 20001213 |                 |          |
|      | US 2001-278250P | P    | 20010323 |                 |          |
|      | US 2001-933894  | A2   | 20010821 |                 |          |

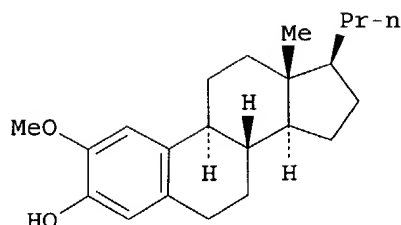
CLASS

| PATENT NO.    | CLASS | PATENT FAMILY CLASSIFICATION CODES  |
|---------------|-------|---|
| US 2002082433 | ICM   | C07J041-00  |
|               | ICS   | C07J043-00; C07J001-00; A61K031-704; A61K031-58;<br>A61K031-56; C07C247-00; A61K031-655; C07J009-00 |

OS NCL 552544000  
 MARPAT 137:47357  
 GI



I



II

AB 2-Methoxyestradiol derivs. of formula I [R1, R4 = H, halo, CN, alkyl, OH, NH2, etc.; R2 = N3, CN, OMe, alkenyl, alkynyl, alkoxy, NH2, etc.; R3 = OH, OAc; R5 = alkyl, alkenyl, (di)alkylamino, OH, alkylene, etc.; R6, R7 = H, alkyl, alkenyl, alkynyl, halo, etc.] are prepared for treating mammalian disease characterized by undesirable angiogenesis. Thus, II was prepared from 2-methoxyestradiol and propyltriphenylphosphonium bromide. The IC50 of II against MDA-MB-231 breast tumor cells was 51.31  $\mu$ M.

ST methoxyestradiol deriv prepn antiangiogenic; estradiol deriv prepn antiangiogenic; antitumor methoxyestradiol deriv prepn; antimitotic methoxyestradiol deriv prepn

IT Structure-activity relationship  
 (antitumor; preparation of 2-methoxyestradiol derivs. as antiangiogenic agents)

IT Mitosis  
 (inhibitors; preparation of 2-methoxyestradiol derivs. as antiangiogenic agents)

IT Angiogenesis inhibitors  
 Antitumor agents  
 Human  
 Mammary gland, neoplasm  
 Neoplasm  
 (preparation of 2-methoxyestradiol derivs. as antiangiogenic agents)

IT 362-07-2, 2-Methoxyestradiol  
 RL: PAC (Pharmacological activity); RCT (Reactant); BIOL (Biological study); RACT (Reactant or reagent)  
 (preparation of 2-methoxyestradiol derivs. as antiangiogenic agents)

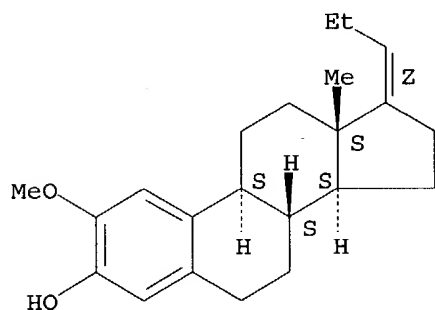
IT 53-63-4P, Estra-1,3,5(10)-trien-3-ol 6301-87-7P **431901-72-3P**  
**431901-73-4P 431901-75-6P 431901-77-8P 431901-91-6P**  
 RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)  
 (preparation of 2-methoxyestradiol derivs. as antiangiogenic agents)

IT 1818-12-8P 4953-96-2P 6298-51-7P 6599-97-9P 7291-57-8P  
 10332-20-4P 32162-96-2P 41259-43-2P 94440-60-5P 165619-07-8P  
 165881-61-8P 229486-18-4P 431901-68-7P 431901-69-8P 431901-70-1P  
 431901-71-2P 431901-74-5P 431901-78-9P 431901-87-0P 431901-90-5P  
 431901-92-7P 431901-93-8P 431901-94-9P 431901-95-0P 431901-96-1P  
 431901-97-2P 431901-98-3P 431901-99-4P 431902-00-0P 431902-01-1P  
 431902-02-2P 431902-03-3P 431902-04-4P 431902-05-5P 431902-06-6P  
 431902-07-7P 431902-08-8P 431902-09-9P **438044-29-2P**  
 438044-30-5P 438044-35-0P  
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES

(Uses)

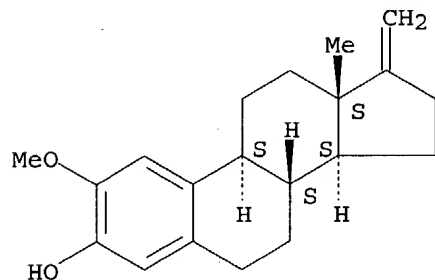
- (preparation of 2-methoxyestradiol derivs. as antiangiogenic agents)
- IT 53-16-7, Estrone, reactions 106-95-6, Allyl bromide, reactions 1779-51-7, Butyltriphenylphosphonium bromide 4784-77-4, Crotyl bromide 5815-08-7 6228-47-3, Propyltriphenylphosphonium bromide
- RL: RCT (Reactant); RACT (Reactant or reagent)
- (preparation of 2-methoxyestradiol derivs. as antiangiogenic agents)
- IT 26356-54-7P 26357-07-3P 93949-26-9P 431901-79-0P 431901-81-4P 431901-82-5P 431901-83-6P 431901-84-7P 431901-85-8P 431901-89-2P 438044-31-6P 438044-32-7P 438044-33-8P
- RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
- (preparation of 2-methoxyestradiol derivs. as antiangiogenic agents)
- IT 431901-72-3P 431901-73-4P 431901-75-6P
- RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
- (preparation of 2-methoxyestradiol derivs. as antiangiogenic agents)
- RN 431901-72-3 HCAPLUS
- CN Estra-1,3,5(10)-trien-3-ol, 2-methoxy-17-propylidene-, (17Z)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.  
Double bond geometry as shown.



- RN 431901-73-4 HCAPLUS
- CN Estra-1,3,5(10)-trien-3-ol, 2-methoxy-17-methylene- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



- RN 431901-75-6 HCAPLUS
- CN 19-Norpregna-1,3,5(10),17(20)-tetraen-3-ol, 2-methoxy- (9CI) (CA INDEX NAME)

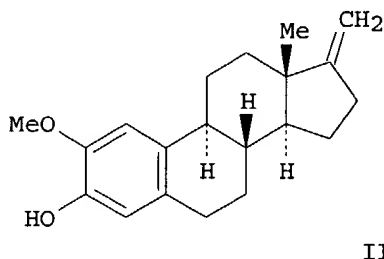
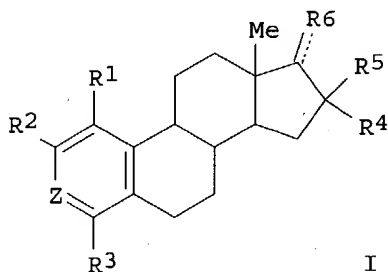
Absolute stereochemistry.  
Double bond geometry unknown.

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 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG  
 AU 2001088386 A5 20020603 AU 2001-88386 20010824  
 EP 1343803 A2 20030917 EP 2001-968112 20010824  
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR  
 PRAI US 2000-253385P P 20001127  
 US 2000-255302P P 20001213  
 US 2001-278250P P 20010323  
 US 2001-933894 A 20010821  
 WO 2001-US26490 W 20010824

## CLASS

| PATENT NO.    | CLASS | PATENT FAMILY CLASSIFICATION CODES |
|---------------|-------|------------------------------------|
| WO 2002042319 | ICM   | C07J001-00                         |

OS MARPAT 137:6309  
 GI



- AB 2-Methoxyestradiol analogs, such as I [R1, R3 = H, halo, CN, alkyl, OH, CH2OH, NH2, alkylamino; R2 = N3, CN, C.tplbond.CR, C=CHR, C.tplbond.CH, OR, amino; R = H, alkyl; Z = COH, COAc; dashed bond = single bond or double bond; R6 = H, OH, O, oxime, amino, alkyl, alkenyl; R4, R5 = H, alkyl, alkenyl, alkynyl], were prepared for treating mammalian disease characterized by undesirable angiogenesis. Thus, 2-methoxyestradiol analog II was prepared by the reaction of methyltriphenylphosphonium bromide and 2-methoxyestrone. In vitro evaluation against MDA-MB-231 breast tumor cells and HUVEC endothelial cells, II showed IC50 0.24±0 and 0.19±0.19 resp.
- ST methoxyestradiol deriv prepn antiangiogenic antitumor; estradiol methoxy deriv prepn antiangiogenic antitumor
- IT Cell proliferation  
 (inhibition; preparation of 2-methoxyestradiol derivs. as antiangiogenic agents)
- IT Mammary gland, neoplasm  
 (inhibitors; preparation of 2-methoxyestradiol derivs. as antiangiogenic agents)
- IT Antitumor agents  
 (mammary gland; preparation of 2-methoxyestradiol derivs. as antiangiogenic agents)
- IT Angiogenesis inhibitors  
 Human

(preparation of 2-methoxyestradiol derivs. as antiangiogenic agents)

IT Estrogens  
 RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(preparation of 2-methoxyestradiol derivs. as antiangiogenic agents)

IT 53-63-4P, Estra-1,3,5(10)-trien-3-ol **431901-72-3P**  
**431901-73-4P 431901-75-6P 431901-77-8P 431901-83-6P**  
**431901-89-2P 431901-91-6P**  
 RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(preparation of 2-methoxyestradiol derivs. as antiangiogenic agents)

IT 1818-12-8P 4953-96-2P 6298-51-7P 6301-87-7P 6599-97-9P  
 7291-57-8P 10332-20-4P 32162-96-2P 41259-43-2P 94440-60-5P  
 165619-07-8P 165881-61-8P 192062-02-5P 229486-18-4P 431901-68-7P  
 431901-69-8P 431901-70-1P 431901-71-2P 431901-74-5P 431901-76-7P  
 431901-78-9P 431901-82-5P 431901-84-7P 431901-86-9P 431901-87-0P  
 431901-88-1P 431901-92-7P 431901-93-8P 431901-94-9P 431901-95-0P  
 431901-96-1P 431901-97-2P 431901-98-3P 431901-99-4P 431902-00-0P  
 431902-01-1P 431902-02-2P 431902-03-3P 431902-04-4P 431902-05-5P  
 431902-06-6P 431902-07-7P 431902-08-8P 431902-09-9P  
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of 2-methoxyestradiol derivs. as antiangiogenic agents)

IT 53-16-7, Estrone, reactions 64-18-6, Formic acid, reactions 100-39-0, Benzyl bromide 106-95-6, Allyl bromide, reactions 362-07-2, 2-Methoxyestradiol 1530-32-1, Ethyl triphenylphosphonium bromide 1779-49-3, Methyl triphenylphosphonium bromide 1779-51-7, Butyl triphenylphosphonium bromide 4784-77-4, Crotyl bromide 5815-08-7, tert-Butoxy bis(dimethylamino)methane 6228-47-3, Propyl triphenylphosphonium bromide 17640-15-2, Methyl cyanofomate  
 RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of 2-methoxyestradiol derivs. as antiangiogenic agents)

IT 26356-54-7P 26357-07-3P 93949-26-9P 431901-79-0P 431901-80-3P  
 431901-81-4P 431901-85-8P 431901-90-5P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

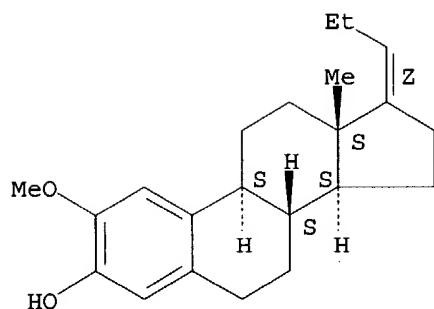
(preparation of 2-methoxyestradiol derivs. as antiangiogenic agents)

IT **431901-72-3P 431901-73-4P 431901-75-6P**  
 RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(preparation of 2-methoxyestradiol derivs. as antiangiogenic agents)

RN 431901-72-3 HCAPLUS  
 CN Estra-1,3,5(10)-trien-3-ol, 2-methoxy-17-propylidene-, (17Z)- (9CI) (CA INDEX NAME)

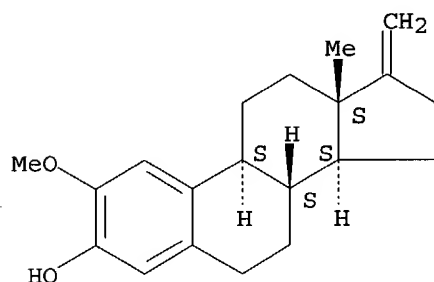
Absolute stereochemistry.  
 Double bond geometry as shown.



RN 431901-73-4 HCAPLUS

CN Estradiol-1,3,5(10)-triene-3-ol, 2-methoxy-17-methylene- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

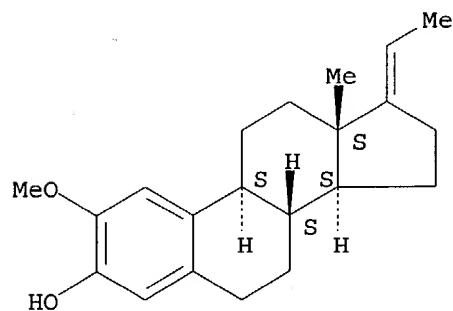


RN 431901-75-6 HCAPLUS

CN 19-Norpregna-1,3,5(10),17(20)-tetraen-3-ol, 2-methoxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

Double bond geometry unknown.



L20 ANSWER 6 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2001:833342 HCAPLUS

DN 135:358085

ED Entered STN: 16 Nov 2001

TI Preparation of 2-substituted pregna-1,3,5(10)-triene and chola-1,3,5(10)-triene derivatives with antiproliferative and antiangiogenic activity

IN Hesse, Robert Henry; Setty, Sundara Katugam Srinivasasetty; Pechet, Maurice Murdoch; Gile, Michael

PA Marsden, John Christopher, UK; Research Institute for Medicine and Chemistry Inc.



SO PCT Int. Appl., 40 pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
 IC ICM C07J041-00  
 ICS A61K031-57; C07J009-00; C07J013-00; C07J051-00; A61K031-575;  
 A61P005-30; A61P035-00  
 CC 32-5 (Steroids)  
 Section cross-reference(s): 1, 63

FAN.CNT 1

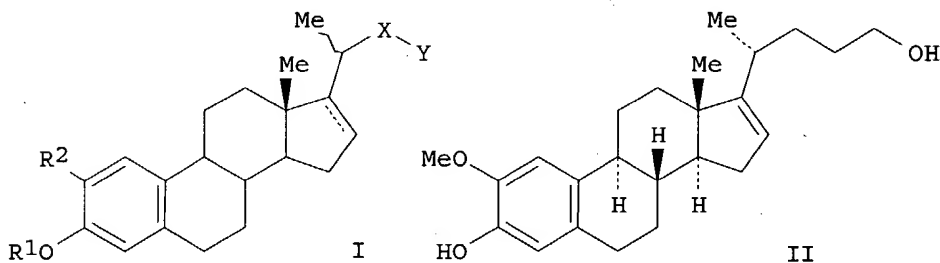
|      | PATENT NO.  | KIND | DATE     | APPLICATION NO. | DATE     |
|------|---|------|----------|-----------------|----------|
| PI   | WO 2001085755   | A1   | 20011115 | WO 2001-GB2103  | 20010511 |
|      | W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM |      |          |                 |          |
|      | RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG  |      |          |                 |          |
|      | EP 1287017  | A1   | 20030305 | EP 2001-928120  | 20010511 |
|      | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR   |      |          |                 |          |
|      | JP 2003532737   | T2   | 20031105 | JP 2001-582354  | 20010511 |
|      | NZ 523042   | A    | 20040528 | NZ 2001-523042  | 20010511 |
|      | NO 2002005392   | A    | 20030109 | NO 2002-5392    | 20021111 |
|      | US 2003158167   | A1   | 20030821 | US 2003-275257  | 20030313 |
| PRAI | US 2000-203462P   | P    | 20000511 |                 |          |
|      | WO 2001-GB2103  | W    | 20010511 |                 |          |

## CLASS

| PATENT NO.    | CLASS | PATENT FAMILY CLASSIFICATION CODES  |
|---------------|-------|---|
| WO 2001085755 | ICM   | C07J041-00  |
|               | ICS   | A61K031-57; C07J009-00; C07J013-00; C07J051-00; A61K031-575; A61P005-30; A61P035-00 |

OS MARPAT 135:358085

GI



AB Compds. of formula I [R1 = H, protecting group; R2 = OH, alkoxy, CHO, alkenyl, etc.; X = alkylene, bond; Y = CHO, (substituted) CH2OH, etc.] are prepared which exhibit potent cell modulating activity, including antiproliferative and antiangiogenic effects. Thus, 2-methoxy-3-triisopropylsilyloxy-19-norpregn-1,3,5(10),17(20)Z-tetraene (preparation given) is reacted with Me acrylate, reduced with LiAlH4, and desilylated with TBAF to give II.

ST pregnatriene deriv prepn antiproliferative antiangiogenic; cholatriene deriv prepn antiproliferative antiangiogenic; antiproliferative

pregnatriene cholatriene deriv; antiangiogenic pregnatriene cholatriene deriv

IT Angiogenesis inhibitors  
Antitumor agents  
(preparation of 2-substituted pregnatriene and cholatriene derivs. with antiproliferative and antiangiogenic activity)

IT Proliferation inhibition  
(proliferation inhibitors; preparation of 2-substituted pregnatriene and cholatriene derivs. with antiproliferative and antiangiogenic activity)

IT 372952-25-5P 372952-27-7P 372952-29-9P 372952-30-2P  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)  
(preparation of 2-substituted pregnatriene and cholatriene derivs. with antiproliferative and antiangiogenic activity)

IT 372952-23-3P 372952-24-4P 372952-28-8P 372952-31-3P 372952-32-4P  
372952-33-5P 372952-34-6P 372952-35-7P 372952-36-8P 372952-37-9P  
372952-38-0P 372952-39-1P 372952-40-4P 372952-41-5P 372952-42-6P  
372952-43-7P 372952-44-8P 372952-45-9P  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(preparation of 2-substituted pregnatriene and cholatriene derivs. with antiproliferative and antiangiogenic activity)

IT 96-33-3, Methyl acrylate 305812-67-3 372952-58-4  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(preparation of 2-substituted pregnatriene and cholatriene derivs. with antiproliferative and antiangiogenic activity)

IT 229486-17-3P 305812-87-7P 305812-89-9P 305812-91-3P  
305812-97-9P 372952-46-0P 372952-47-1P 372952-48-2P 372952-49-3P  
372952-50-6P 372952-51-7P 372952-52-8P 372952-53-9P 372952-54-0P  
372952-55-1P 372952-56-2P 372952-57-3P  
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
(preparation of 2-substituted pregnatriene and cholatriene derivs. with antiproliferative and antiangiogenic activity)

RE.CNT 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

- (1) Cushman, M; JOURNAL OF MEDICINAL CHEMISTRY 1995, V38(12), P2041 HCAPLUS
- (2) Marsden, J; WO 0068246 A 2000 HCAPLUS
- (3) Mitsubishi Chemical Industries Co Ltd; JP 54112849 A HCAPLUS
- (4) Mitsubishi Chemical Industries Co Ltd; JP 54112850 A HCAPLUS
- (5) Mitsubishi Chemical Industries Co Ltd; JP 54117454 A HCAPLUS
- (6) Mitsubishi Chemical Industries Co Ltd; JP 54117455 A HCAPLUS
- (7) Mitsubishi Chemical Industries Co Ltd; JP 54117456 A HCAPLUS
- (8) Mitsubishi Chemical Industries Co Ltd; JP 54112849 A 1979 HCAPLUS
- (9) Mitsubishi Chemical Industries Co Ltd; JP 54112850 A 1979 HCAPLUS
- (10) Mitsubishi Chemical Industries Co Ltd; JP 54117454 A 1979 HCAPLUS
- (11) Mitsubishi Chemical Industries Co Ltd; JP 54117455 A 1979 HCAPLUS
- (12) Mitsubishi Chemical Industries Co Ltd; JP 54117456 A 1979 HCAPLUS
- (13) Mitsubishi Chemical Industries Co Ltd; PATENT ABSTRACTS OF JAPAN 1979, V003(133), PC-063
- (14) Mitsubishi Chemical Industries Co Ltd; PATENT ABSTRACTS OF JAPAN 1979, V003(133), PC-063
- (15) Ruggieri, P; US 3562260 A 1971 HCAPLUS

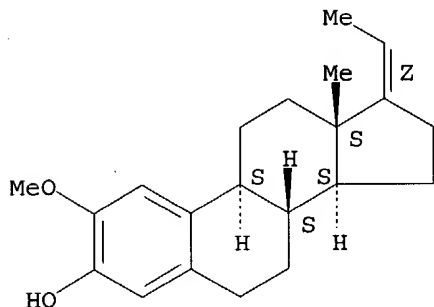
IT 229486-17-3P  
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
(preparation of 2-substituted pregnatriene and cholatriene derivs. with antiproliferative and antiangiogenic activity)

RN 229486-17-3 HCAPLUS

CN 19-Norpregna-1,3,5(10),17(20)-tetraen-3-ol, 2-methoxy-, (17Z)- (9CI) (CA

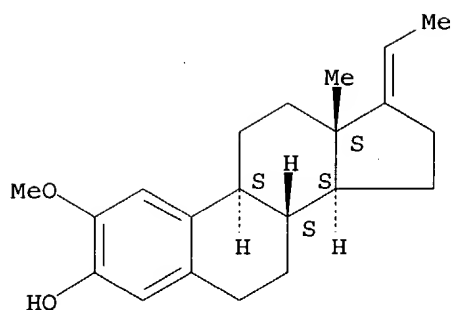
## INDEX NAME)

Absolute stereochemistry.  
Double bond geometry as shown.



L20 ANSWER 7 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN  
AN 2000:814500 HCAPLUS  
DN 133:350395  
ED Entered STN: 21 Nov 2000  
TI Synthesis of cholestane compounds with a c17-alkyl side chain and an  
aromatic A-ring for use in cell modulating therapy  
IN Hesse, Robert Henry; Setty, Sundara Katugam Srinivasasetty; Ramgopal,  
Malathi; Kugabalusooriar, Sanga  
PA Marsden, John, Christopher, UK; Research Institute for Medicine and  
Chemistry Inc.  
SO PCT Int. Appl., 75 pp.  
CODEN: PIXXD2  
DT Patent  
LA English  
IC ICM C07J009-00  
ICS C07J041-00; A61K031-575; C07J051-00; A61P017-02; A61P019-08;  
A61P037-06; A61P029-00; A61P035-00; A61P021-00; A61P009-10;  
A61P005-20; A61P017-00; A61P009-12; A61P019-02; A61P011-06;  
A61P025-28; A61P015-18; A61P007-02; A61P003-06  
CC 32-7 (Steroids)  
Section cross-reference(s): 1, 2  
FAN.CNT 1

| PATENT NO.  | KIND | DATE     | APPLICATION NO. | DATE     |
|---|------|----------|-----------------|----------|
| WO 2000068246   | A1   | 20001116 | WO 2000-GB1813  | 20000511 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN,<br>CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB,<br>GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR,<br>KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO,<br>NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT,<br>TZ, UA, UG, US, VZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU,<br>TJ, TM<br>RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE,<br>DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF,<br>CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG |      |          |                 |          |
| EP 1179005  | A1   | 20020213 | EP 2000-927569  | 20000511 |
| EP 1179005  | B1   | 20031119 |                 |          |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,<br>IE, SI, LT, LV, FI, RO  |      |          |                 |          |
| AT 254629   | E    | 20031215 | AT 2000-927569  | 20000511 |
| PT 1179005  | T    | 20040430 | PT 2000-927569  | 20000511 |
| NZ 515482   | A    | 20040528 | NZ 2000-515482  | 20000511 |
| ES 2207509  | T3   | 20040601 | ES 2000-927569  | 20000511 |
| ZA 2001009272   | A    | 20021128 | ZA 2001-9272    | 20011109 |



IT 438044-29-2P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

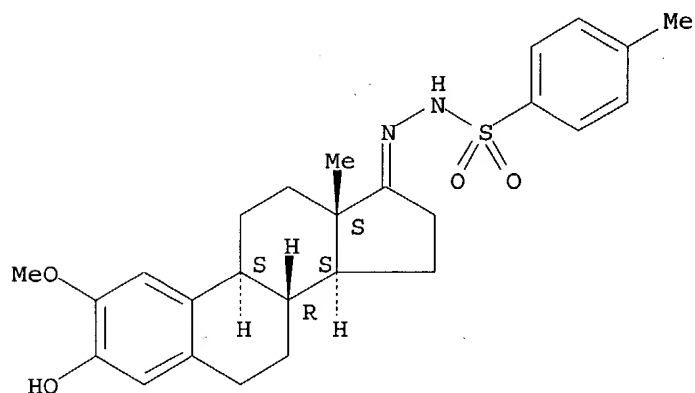
(preparation of 2-methoxyestradiol derivs. as antiangiogenic agents)

RN 438044-29-2 HCAPLUS

CN Benzenesulfonic acid, 4-methyl-, (3-hydroxy-2-methoxyestra-1,3,5(10)-trien-17-ylidene)hydrazide (9CI) (CA INDEX NAME)

Absolute stereochemistry.

Double bond geometry unknown.



L20 ANSWER 5 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2002:408687 HCAPLUS

DN 137:6309

ED Entered STN: 31 May 2002

TI Preparation of 2-methoxyestradiol analogs as antiangiogenic agents

IN Agoston, Gregory; Shah, Jamshed H.; Hunsucker, Kimberly A.; Pribluda, Victor; Lavallee, Theresa M.; Green, Shawn J.; Herbstritt, Christopher J.; Zhan, Xiaoguo H.; Treston, Anthony

PA Entremed, Inc., USA

SO PCT Int. Appl., 86 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM C07J001-00

CC 32-3 (Steroids)

Section cross-reference(s): 1, 2, 63

FAN.CNT 2

|    | PATENT NO.    | KIND | DATE     | APPLICATION NO. | DATE     |
|----|---------------|------|----------|-----------------|----------|
| PI | WO 2002042319 | A2   | 20020530 | WO 2001-US26490 | 20010824 |

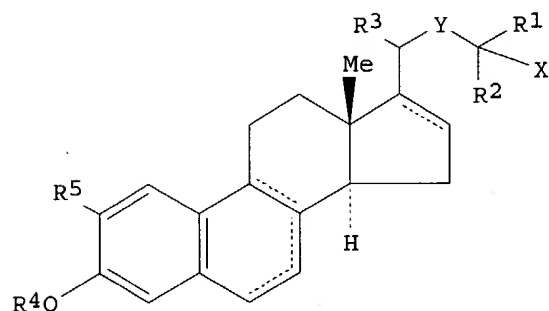
|                    |   |          |              |          |
|--------------------|---|----------|--------------|----------|
| NO 2001005520      | A | 20020109 | NO 2001-5520 | 20011112 |
| PRAI GB 1999-10934 | A | 19990511 |              |          |
| WO 2000-GB1813     | W | 20000511 |              |          |

## CLASS

| PATENT NO.    | CLASS | PATENT FAMILY CLASSIFICATION CODES  |
|---------------|-------|---|
| WO 2000068246 | ICM   | C07J009-00  |
|               | ICS   | C07J041-00; A61K031-575; C07J051-00; A61P017-02;<br>A61P019-08; A61P037-06; A61P029-00; A61P035-00;<br>A61P021-00; A61P009-10; A61P005-20; A61P017-00;<br>A61P009-12; A61P019-02; A61P011-06; A61P025-28;<br>A61P015-18; A61P007-02; A61P003-06 |

OS MARPAT 133:350395

GI



I

- AB Synthesis of cholestane compds. (I) [R1 and R2, which may be the same or different, = alkyl, alkenyl, alkynyl; R3 = Me having  $\alpha$ - or  $\beta$ -configuration; R4 = H or an etherifying or esterifying group; R5 = H, OH, alkoxy; X = OR4, wherein R4 is as defined above, or NR6R7 wherein R6 = H, aliphatic or araliph. organic group, acyl group comprising aliphatic, araliph. or aryl organic group linked to the nitrogen atom by way of a carbonyl group; R7 = H, alkyl; Y = (un)substituted alkylene, alkenylene, alkynylene; dotted lines signify that double bonds may be present at the 16(17)-position and/or either at the 6(7)- and 8(9)-positions or at the 7(8)-position] is disclosed for modulation of cell growth and differentiation, while having low calcemic activity. Thus, I [R1,R2 = Me; R3 =  $\alpha$ -Me; R4,R5 = H; X = NHAc; Y = (CH2)4;  $\Delta$ 16 double bond] is prepared by reaction of 3-triisopropylsilyloxy-19-norchol-1,3,5(10),16-tetraene-24-bromide with acetonitrile followed by reduction of nitrile to amine, methylation of amine with Me lithium, acetylation of the amino with acetic anhydride and desilylation with TBAF.
- ST cholestane analog prepn cell growth modulation differentiation; low calcemic activity cholestane analog
- IT Steroids, preparation  
Steroids, preparation  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(aromatic; synthesis of cholestane compds. with a c17-alkyl side chain and an aromatic A-ring for use in cell modulating therapy)
- IT Transplant and Transplantation  
(host-vs.-graft reaction; synthesis of cholestane compds. with a c17-alkyl side chain and an aromatic A-ring for use in cell modulating therapy)
- IT Arthritis  
(psoriatic arthritis; synthesis of cholestane compds. with a c17-alkyl side chain and an aromatic A-ring for use in cell modulating therapy)
- IT Hyperparathyroidism

(secondary; synthesis of cholestane compds. with a c17-alkyl side chain and an aromatic A-ring for use in cell modulating therapy)

IT Mental disorder  
(senile psychosis; synthesis of cholestane compds. with a c17-alkyl side chain and an aromatic A-ring for use in cell modulating therapy)

IT Heart, disease  
(spondylitic; synthesis of cholestane compds. with a c17-alkyl side chain and an aromatic A-ring for use in cell modulating therapy)

IT Aromatic hydrocarbons, preparation  
Aromatic hydrocarbons, preparation  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(steroids; synthesis of cholestane compds. with a c17-alkyl side chain and an aromatic A-ring for use in cell modulating therapy)

IT Anti-inflammatory agents  
Antitumor agents  
Asthma  
Autoimmune disease  
Blood coagulation  
Bone, disease  
Burn  
Fertility  
Hyperplasia  
Hypertension  
Intestine, disease  
Muscle, disease  
Rheumatoid arthritis  
Skin, disease  
Transplant rejection  
Wound healing  
(synthesis of cholestane compds. with a c17-alkyl side chain and an aromatic A-ring for use in cell modulating therapy)

IT 57-88-5, Cholest-5-en-3-ol (3 $\beta$ )-, biological studies  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(blood reduction; synthesis of cholestane compds. with a c17-alkyl side chain and an aromatic A-ring for use in cell modulating therapy)

IT 9002-64-6, Parathyroid hormone  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(suppression; synthesis of cholestane compds. with a c17-alkyl side chain and an aromatic A-ring for use in cell modulating therapy)

IT 305812-17-3P 305812-18-4P 305812-52-6P  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)  
(synthesis of cholestane compds. with a c17-alkyl side chain and an aromatic A-ring for use in cell modulating therapy)

IT 305812-19-5P 305812-20-8P 305812-21-9P 305812-22-0P 305812-23-1P  
305812-24-2P 305812-25-3P 305812-26-4P 305812-27-5P 305812-28-6P  
305812-29-7P 305812-30-0P 305812-31-1P 305812-32-2P 305812-33-3P  
305812-34-4P 305812-35-5P 305812-36-6P 305812-37-7P 305812-38-8P  
305812-39-9P 305812-40-2P 305812-41-3P 305812-42-4P 305812-43-5P  
305812-44-6P 305812-45-7P 305812-46-8P 305812-47-9P 305812-48-0P  
305812-49-1P 305812-50-4P 305812-51-5P 305812-53-7P 305812-54-8P  
305812-55-9P 305812-56-0P 305812-57-1P 305812-58-2P 305812-59-3P  
305812-60-6P 305812-61-7P 305812-62-8P 305812-63-9P 305812-64-0P  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(synthesis of cholestane compds. with a c17-alkyl side chain and an aromatic A-ring for use in cell modulating therapy)

IT 74-88-4, Methyl iodide, reactions 75-03-6, Ethyl iodide 75-05-8,

Acetonitrile, reactions 78-77-3, Isobutyl bromide 96-33-3 98-88-4,  
Benzoyl chloride 103-80-0, Phenylacetyl chloride 106-96-7, Propargyl  
bromide 474-87-3 517-09-9 867-13-0 922-67-8, Methyl propiolate  
1439-36-7, 1-Triphenylphosphoranylidene-2-propanone 3234-64-8,  
1,1-Diethylpropargylamine 4736-60-1, Ethyl triphenylphosphonium iodide  
7103-48-2, Estrone-3-tetrahydropyranyl ether 17963-41-6 305812-65-1  
305812-66-2 305812-67-3 305812-69-5

RL: RCT (Reactant); RACT (Reactant or reagent)

(synthesis of cholestane compds. with a c17-alkyl side chain and an  
aromatic A-ring for use in cell modulating therapy)

|    |              |              |              |              |              |
|----|--------------|--------------|--------------|--------------|--------------|
| IT | 229486-17-3P | 305812-70-8P | 305812-71-9P | 305812-72-0P |              |
|    | 305812-73-1P | 305812-75-3P | 305812-76-4P | 305812-77-5P | 305812-79-7P |
|    | 305812-81-1P | 305812-83-3P | 305812-85-5P | 305812-87-7P | 305812-89-9P |
|    | 305812-91-3P | 305812-93-5P | 305812-95-7P | 305812-97-9P | 305812-99-1P |
|    | 305813-01-8P | 305813-03-0P | 305813-05-2P | 305813-07-4P | 305813-09-6P |
|    | 305813-10-9P | 305813-12-1P | 305813-14-3P | 305813-15-4P | 305813-16-5P |
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|    | 305813-30-3P | 305813-32-5P | 305813-34-7P | 305813-36-9P | 305813-38-1P |
|    | 305813-39-2P | 305813-40-5P | 305813-41-6P | 305813-42-7P | 305813-43-8P |
|    | 305813-44-9P | 305813-45-0P | 305813-46-1P | 305813-47-2P | 305813-48-3P |
|    | 305813-49-4P | 305813-50-7P | 305813-51-8P | 305813-52-9P | 305813-53-0P |
|    | 305813-54-1P | 305813-55-2P | 305813-56-3P | 305813-57-4P | 305813-58-5P |
|    | 305813-59-6P | 305813-60-9P |              |              |              |

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
(Reactant or reagent)

(synthesis of cholestane compds. with a c17-alkyl side chain and an  
aromatic A-ring for use in cell modulating therapy)

RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

- (1) Escalera; 1993, 7, HCAPLUS
- (2) Escalera; J STEROID BIOCHEM MOL BIOL 1993, V45(4), P257 HCAPLUS
- (3) Laing, S; US 3717627 A 1973
- (4) Lajeunesse; 1994, 23, HCAPLUS
- (5) Lajeunesse; BONE MINER 1994, V24(1), P1 HCAPLUS
- (6) Liel; 1992, 25, HCAPLUS
- (7) Liel; ENDOCRINOLOGY (BALTIMORE) 1992, V130(5), P2597 HCAPLUS
- (8) Mountford; 1999, 8, HCAPLUS
- (9) Mountford; EXP HEMATOL (N Y) 1999, V27(3), P451 HCAPLUS
- (10) Ruggieri, P; US 3562260 A 1971 HCAPLUS

IT 229486-17-3P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
(Reactant or reagent)

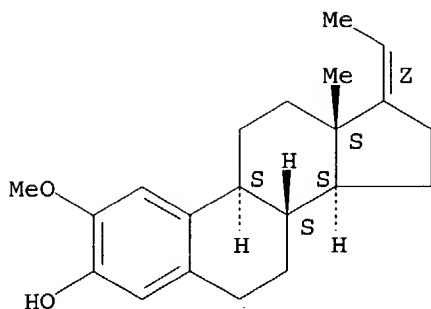
(synthesis of cholestane compds. with a c17-alkyl side chain and an  
aromatic A-ring for use in cell modulating therapy)

RN 229486-17-3 HCAPLUS

CN 19-Norpregna-1,3,5(10),17(20)-tetraen-3-ol, 2-methoxy-, (17Z)- (9CI) (CA  
INDEX NAME)

Absolute stereochemistry.

Double bond geometry as shown.



L20 ANSWER 8 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 1999:460438 HCAPLUS

DN 131:88083

ED Entered STN: 28 Jul 1999

TI Preparation of estrone sulfamate inhibitors of estrone sulfatase

IN Tanabe, Masato; Peters, Richard H.; Chao, Wan-Ru; Shigeno, Kazuhiko

PA SRI International, USA

SO PCT Int. Appl., 102 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM C07J041-00

ICS A61K031-565; A61K031-57; A61K031-575

CC 32-3 (Steroids)

Section cross-reference(s): 2, 63

FAN.CNT 1

|      | PATENT NO.   | KIND | DATE     | APPLICATION NO. | DATE     |
|------|--|------|----------|-----------------|----------|
| PI   | WO 9933858   | A2   | 19990708 | WO 1998-US27333 | 19981221 |
|      | W: AU, CA, JP, KR  |      |          |                 |          |
|      | RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE |      |          |                 |          |
|      | US 6046186   | A    | 20000404 | US 1997-997416  | 19971224 |
|      | CA 2318349   | AA   | 19990708 | CA 1998-2318349 | 19981221 |
|      | AU 9919416   | A1   | 19990719 | AU 1999-19416   | 19981221 |
|      | AU 751732  | B2   | 20020829 |                 |          |
|      | EP 1042354   | A2   | 20001011 | EP 1998-964243  | 19981221 |
|      | EP 1042354   | B1   | 20040303 |                 |          |
|      | R: DE, FR, GB, IT, NL  |      |          |                 |          |
|      | JP 2001527089  | T2   | 20011225 | JP 2000-526534  | 19981221 |
|      | EP 1405860   | A1   | 20040407 | EP 2003-28361   | 19981221 |
|      | R: DE, FR, GB, IT, NL  |      |          |                 |          |
| PRAI | US 1997-997416   | A    | 19971224 |                 |          |
|      | EP 1998-964243   | A3   | 19981221 |                 |          |
|      | WO 1998-US27333  | W    | 19981221 |                 |          |

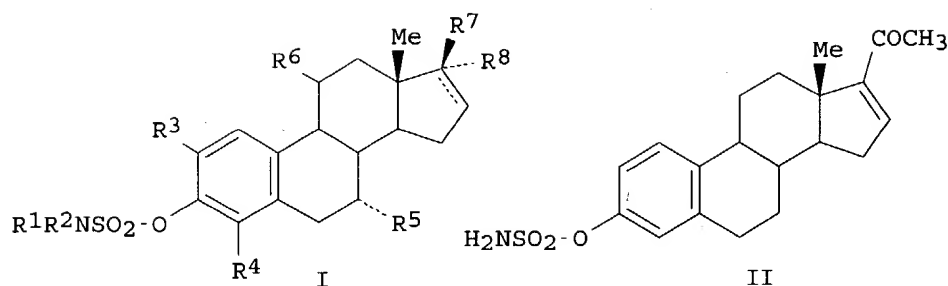
CLASS

| PATENT NO. | CLASS | PATENT FAMILY CLASSIFICATION CODES        |
|------------|-------|---|
| WO 9933858 | ICM   | C07J041-00                                |
|            | ICS   | A61K031-565; A61K031-57; A61K031-575      |
| WO 9933858 | ECLA  | C07J041/00B; C07J041/00C40; C07J041/00C70 |
| US 6046186 | ECLA  | C07J041/00B; C07J041/00C40; C07J041/00C70 |
| EP 1405860 | ECLA  | C07J041/00B; C07J041/00C40; C07J041/00C70 |

OS MARPAT 131:88083

GI





AB Novel compds. of formula I [R1, R2 = H, alkyl, etc.; R3 = H, CN, NO2, COOH, alkoxy, carbonyl, etc.; R4 = H, NO2, (substituted) amino; R5, R6 = H, alkyl; R7, R8 = H, alkyl, alkenyl, alkynyl, alkoxy, acyl, acyloxy, etc.; R7, R8 = oxo, alkylidene, etc.] are prepared as inhibitors of estrone sulfatase. Thus, II is prepared from ethynylestradiol in 4 steps. and showed estrone sulfatase inhibitory activity of IC50 = 21 pM. Pharmaceutical compns. and methods for using I to treat estrogen-dependent disorders are provided.

ST estrone sulfamate prepn estrone sulfatase inhibitor

IT Estrogens  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(antiestrogens; preparation of estrone sulfamates as inhibitors of estrone sulfatase)

IT Antitumor agents  
(preparation of estrone sulfamates as inhibitors of estrone sulfatase)

IT 59298-96-3, Estrone sulfatase  
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
(inhibitors; preparation of estrone sulfamates as inhibitors of estrone sulfatase)

IT 185910-34-3P 185910-42-3P 208924-86-1P 208924-87-2P 229485-78-3P  
229485-79-4P 229485-80-7P 229485-81-8P 229485-82-9P 229485-83-0P  
229485-84-1P 229485-85-2P 229485-86-3P 229485-87-4P 229485-88-5P  
229485-89-6P 229485-90-9P 229485-91-0P 229485-92-1P 229485-93-2P  
229485-94-3P 229485-95-4P 229485-96-5P 229485-97-6P 229485-98-7P  
229485-99-8P 229486-00-4P 229486-01-5P 229486-02-6P 229486-03-7P  
229486-04-8P 229486-05-9P  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(preparation of estrone sulfamates as inhibitors of estrone sulfatase)

IT 50-28-2, Estradiol, reactions 53-16-7, Estrone, reactions 57-63-6, Ethynylestradiol 108-01-0, N,N-Dimethylethanolamine 109-77-3, Malononitrile 362-08-3 867-13-0, Triethylphosphonoacetate 1779-51-7, Butyltriphenylphosphonium bromide 4584-46-7 5407-04-5 6228-47-3, Propyltriphenylphosphonium bromide 7678-95-7 67530-18-1 229486-27-5  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(preparation of estrone sulfamates as inhibitors of estrone sulfatase)

IT 858-98-0P 1667-98-7P 4736-62-3P 5774-17-4P 5779-47-5P 5976-73-8P  
5976-74-9P 6599-97-9P 13879-55-5P 13879-57-7P 14030-45-6P  
14846-63-0P 14982-15-1P 15001-40-8P 22787-09-3P 23880-59-3P  
31559-52-1P 57711-40-7P 59077-04-2P, 19-Norpregna-1,3,5(10)-trien-3-ol  
59452-15-2P 59452-16-3P, 19,21-Dinorchola-1,3,5(10)-trien-3-ol  
64215-82-3P 67519-62-4P 71716-18-2P 96111-26-1P 101766-63-6P  
115208-23-6P 115387-92-3P 116627-15-7P 116627-20-4P 120574-27-8P  
120574-28-9P 165619-18-1P 165619-19-2P 165619-20-5P 185910-40-1P  
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208758-50-3P 229486-06-0P 229486-07-1P 229486-08-2P 229486-09-3P

229486-10-6P 229486-11-7P 229486-12-8P 229486-13-9P 229486-14-0P  
 229486-15-1P 229486-16-2P **229486-17-3P** 229486-18-4P  
 229486-19-5P 229486-20-8P 229486-21-9P 229486-22-0P 229486-23-1P  
 229486-24-2P 229486-25-3P 229486-26-4P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
 (Reactant or reagent)

(preparation of estrone sulfamates as inhibitors of estrone sulfatase)

IT **229486-17-3P**

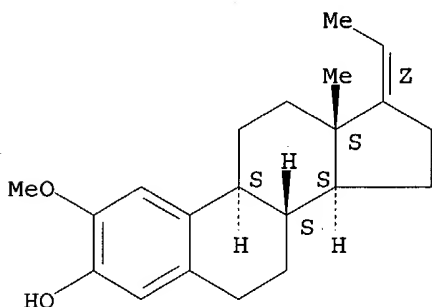
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
 (Reactant or reagent)

(preparation of estrone sulfamates as inhibitors of estrone sulfatase)

RN 229486-17-3 HCAPLUS

CN 19-Norpregna-1,3,5(10),17(20)-tetraen-3-ol, 2-methoxy-, (17Z)- (9CI) (CA  
 INDEX NAME)

Absolute stereochemistry.  
 Double bond geometry as shown.



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FILE 'USPATFULL' ENTERED AT 15:14:20 ON 05 SEP 2004

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L21 ANSWER 1 OF 4 USPATFULL on STN

AN 2004:2032 USPATFULL

TI Systems and methods for rapid evaluation and design of molecules for  
 predicted biological activity

IN Hendry, Lawrence B., Augusta, GA, UNITED STATES

PI US 2004002052 A1 20040101

AI US 2002-279546 A1 20021023 (10)

PRAI US 2001-344560P 20011023 (60)

US 2001-339954P 20011210 (60)

DT Utility

FS APPLICATION

LREP JOHN S. PRATT, ESQ, KILPATRICK STOCKTON, LLP, 1100 PEACHTREE STREET,  
 SUITE 2800, ATLANTA, GA, 30309

CLMN Number of Claims: 38

ECL Exemplary Claim: 1

DRWN 16 Drawing Page(s)

LN.CNT 2883

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The computer-based systems and methods are for rapidly evaluating  
 molecules for suspected biological activity and relative potency, and  
 for designing molecules for desired biological activity. The systems and

methods enable rapid screening of large molecular databases using one or more search engines designed to identify molecules predicted to possess specific biological activities.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

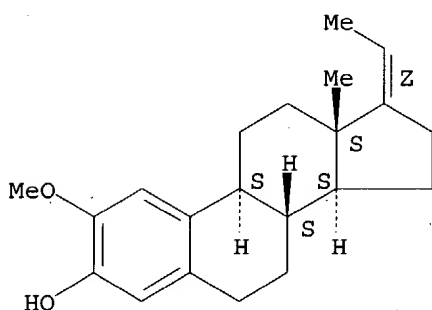
IT 229486-17-3 431901-73-4

(as standard in construction of search engine for evaluation of substances for predicted antiangiogenic activity; systems and methods for rapid evaluation and design of mols. for predicted biol. activity)

RN 229486-17-3 USPTAFULL

CN 19-Norpregna-1,3,5(10),17(20)-tetraen-3-ol, 2-methoxy-, (17Z)- (9CI) (CA INDEX NAME)

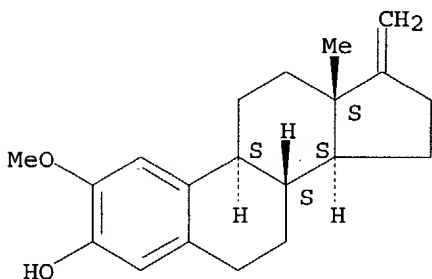
Absolute stereochemistry.  
Double bond geometry as shown.



RN 431901-73-4 USPTAFULL

CN Estra-1,3,5(10)-trien-3-ol, 2-methoxy-17-methylene- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L21 ANSWER 2 OF 4 USPTAFULL on STN

AN 2003:226354 USPTAFULL

TI 2-substituted pregna-1,3,5(10) triene and chola-1,3,5(10) triene derivatives and their biological activity

IN Hesse, Robert Henry, Winchester, MA, UNITED STATES

Setty, Sundara Katugam Srinivasasetty, Cambridge, MA, UNITED STATES

Pechet, Maurice Murdoch, Cambridge, MA, UNITED STATES

Gile, Michael, Methuen, MA, UNITED STATES

PI US 2003158167 A1 20030821

AI US 2003-275257 A1 20030313 (10)

WO 2001-GB2103 20010511

DT Utility

FS APPLICATION

LREP BACON & THOMAS, PLLC, 625 SLATERS LANE, FOURTH FLOOR, ALEXANDRIA, VA, 22314

CLMN Number of Claims: 13

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 978

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compounds of formula (I) in which: R.sup.1 represents a hydrogen atom or an O-protecting group; R.sup.2 represents a hydroxyl, lower alkoxy, carboxaldehyde, lower alk-1-enyl or hydroxy- or lower alkoxy-substituted lower alkyl group; R.sup.3 represents a methyl group having  $\alpha$ - or  $\beta$ -configuration; X represents a C.sub.1-3 alkylene group or a valence bond; Y represents a carboxaldehyde group or a group of formula --C(R.sup.4)(R.sup.5)OR.sup.1 where R.sup.1 is as defined above and R.sup.4 and R.sup.5, which may be the same or different, are each selected from hydrogen atoms, alkyl, alkenyl and alkynyl groups such that the total carbon content of R.sup.4 and R.sup.5 does not exceed three atoms, with the proviso that X is a valence bond when both R.sup.4 and R.sup.5 are other than hydrogen; and the dotted line signifies that a double bond may optionally be present at the 16(17)-position exhibit potent cell modulating activity, including antiproliferative and antiangiogenic effects.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT 229486-17-3P

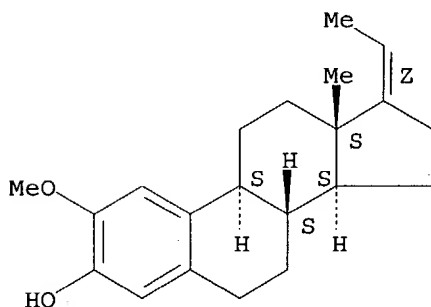
(preparation of 2-substituted pregnatriene and cholatriene derivs. with antiproliferative and antiangiogenic activity)

RN 229486-17-3 USPTAFULL

CN 19-Norpregna-1,3,5(10),17(20)-tetraen-3-ol, 2-methoxy-, (17Z)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

Double bond geometry as shown.



L21 ANSWER 3 OF 4 USPTAFULL on STN

AN 2002:157823 USPTAFULL

TI Antiangiogenic agents

IN Agoston, Gregory E., Germantown, MD, UNITED STATES

Shah, Jamshed H., Brookeville, MD, UNITED STATES

Hunsucker, Kimberly A., Germantown, MD, UNITED STATES

Pribluda, Victor S., Silver Spring, MD, UNITED STATES

LaVallee, Theresa M., Rockville, MD, UNITED STATES

Green, Shawn J., Vienna, VA, UNITED STATES

Herbstritt, Christopher J., Rockville, VA, UNITED STATES

Zhan, Xiaoguo H., Montgomery Village, MD, UNITED STATES

Treston, Anthony M., Rockville, MD, UNITED STATES

PI US 2002082433 A1 20020627

AI US 2001-939208 A1 20010824 (9)

RLI Continuation-in-part of Ser. No. US 2001-933894, filed on 21 Aug 2001,  
PENDING Continuation-in-part of Ser. No. US 2000-641327, filed on 18 Aug  
2000, PENDING

PRAI US 2000-253385P 20001127 (60)



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Dossier: 10002399

Legal Date: 12-03-2004

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| 3   | IMIS   | 2               |
| 4   | DISQ   | 1               |

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